

International Painful Bladder Foundation

The IPBF is a voluntary non-profit organization focused on interstitial cystitis/bladder pain syndrome/hypersensitive bladder/Hunner lesion
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RESEARCH UPDATE February 2022

A REVIEW OF SELECTED RECENT SCIENTIFIC LITERATURE ON INTERSTITIAL CYSTITIS, BLADDER PAIN SYNDROME, HUNNER LESION, HYPERSENSITIVE BLADDER, CHRONIC (PELVIC) PAIN, ASSOCIATED DISORDERS AND KETAMINE CYSTITIS.

Most of these have a direct link to the PubMed abstract if you click on the title. An increasing number of scientific articles "In Press" or "Early View" are being published early online (on the Journal website) as "Epub ahead of print" sometimes long before they are published in the journals. While abstracts are usually available on PubMed, the pre-publication articles can only be read online if you have online access to that specific journal. However, in some cases there may be [free access](#) to the full article online. Click on the title to go to the PubMed abstract or to the full article in the case of free access.

Terminology: different published articles use different terminology, for example: interstitial cystitis, painful bladder syndrome, (primary) bladder pain syndrome, hypersensitive bladder, chronic pelvic pain (syndrome) or combinations of these. Hunner's ulcer, Hunner lesion, Hunner IC and Classic IC are synonymous. When reviewing the article, we use the terminology used by the authors.

NIH MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN (MAPP) RESEARCH NETWORK (For more information about the MAPP Research Network, [click here](#))

[THE URINARY PROTEOMIC PROFILE IMPLICATES KEY REGULATORS FOR UROLOGIC CHRONIC PELVIC PAIN SYNDROME \(UCPPS\): A MAPP RESEARCH NETWORK STUDY](#)

John W Froehlich, Hsin-Hsiao Scott Wang, Tanya Logvinenko, Stephen Kostel, Shannon DiMartino, Adrie van Bokhoven, Marsha A Moses, Richard S Lee, MAPP Research Network. *Mol Cell Proteomics*. 2021 Nov 10;100176. doi: 10.1016/j.mcpro.2021.100176. Online ahead of print. PMID: 34774759 DOI: 10.1016/j.mcpro.2021.100176
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Urologic chronic pelvic pain syndrome (UCPPS) is a condition of unknown etiology characterized by pelvic pain, and urinary frequency and/or urgency. As the proximal fluid of this syndrome, urine is an ideal candidate sample matrix for an unbiased study of UCPPS. In this study, a large, discovery-phase, TMT-based quantitative urinary proteomics analysis of 244 subjects was performed. The subjects included patients with UCPPS (n=82), healthy controls (HC) (n=94) and disparate chronic pain diseases, termed positive controls (PC) (n=68). Utilizing training and testing cohorts, the authors identified and validated a small and distinct set of proteins that distinguished UCPPS from HC (n=9) and UCPPS from PC (n=3). Validated UCPPS: HC proteins were predominantly ECM/ECM modifying or immunomodulatory/host defense in nature. Significantly varying proteins in the UCPPS: HC comparison were overrepresented by members of several dysregulated biological processes including decreased immune cell migration, decreased development of epithelial tissue and increased bleeding. Comparison with the PC cohort enabled evaluation of UCPPS-specific upstream regulators, contrasting UCPPS with other conditions that cause chronic pain. Specific to UCPPS were alterations in the predicted signaling of several upstream regulators, including alpha-catenin, IL6, EGF, and TGFB1, among others. These findings advance our knowledge of the etiology of UCPPS and inform potential future clinical translation into a diagnostic panel for UCPPS.

[LONGITUDINAL CHANGES IN THE PELVIC PAIN ONLY AND WIDESPREAD PAIN PHENOTYPES OVER ONE YEAR IN THE MAPP-I UROLOGIC CHRONIC PELVIC PAIN SYNDROME \(UCPPS\) COHORT](#)

H Henry Lai, Emine O Bayman, Michael O Bishop, J Richard Landis, Steven E Harte, J Quentin Clemens, Larissa V Rodriguez, Siobhan Sutcliffe, Bayley J Taple, Bruce D Naliboff, The Mapp Research Network. *Urology*. 2022 Jan

9;S0090-4295(21)01185-7. doi: 10.1016/j.urology.2021.12.016. Online ahead of print. PMID: 35021046 DOI: 10.1016/j.urology.2021.12.016

The purpose of this MAPP study was to examine how often urologic chronic pelvic pain syndrome (UCPPS) patients progressed from Pelvic Pain Only at baseline to Widespread Pain, or vice versa, during one-year longitudinal follow-up. Men and women with UCPPS enrolled in the MAPP-I Epidemiology and Phenotyping Study completed a self-report body map to indicate their locations of pain every 2 months over 12 months. Patients were categorized at each assessment into one of three pain phenotypes: 1) Pelvic Pain Only, 2) an Intermediate group, 3) Widespread Pain. Only patients who completed 3 or more follow-ups were included in this longitudinal analysis. The primary outcome measure was pain classification at the majority ($\geq 60\%$) of follow-up assessments. Longitudinal trends of somatic symptom burden were also assessed. Among the 93 UCPPS participants with Pelvic Pain Only at baseline, only 2% ($n=2$) showed a Widespread Pain phenotype for the majority of assessments over 12 months. Among the 121 participants who had Widespread Pain at baseline, 6% ($n=7$) demonstrated Pelvic Pain Only for the majority of assessments over 12 months. Over half of participants ($\geq 53\%$) stayed in their baseline phenotypic group. Somatic symptom burden remained stable over 12 months for each of the groups with high intra-class correlation coefficient (0.67 to 0.82). It was uncommon for UCPPS patients to progress from Pelvic Pain Only to Widespread Pain, or vice versa, over 12 months. These data suggest that Pelvic Pain Only and Widespread Pain are distinct UCPPS phenotypes that are relatively stable over 12 months of follow up.

CEREBRAL PERFUSION AND SENSORY TESTING RESULTS DIFFER IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS WITH AND WITHOUT FIBROMYALGIA: A SITE-SPECIFIC MAPP NETWORK STUDY

Georg Deutsch, Hrishikesh Deshpande, H Henry Lai, Jason J Kutch, Timothy J Ness. *J Pain Res.* 2021 Dec 23;14:3887-3895. doi: 10.2147/JPR.S343695. eCollection 2021. PMID: 34992450 PMCID: PMC8711634 DOI: 10.2147/JPR.S343695

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Fibromyalgia is a common co-morbidity in patients with interstitial cystitis/bladder pain syndrome. Quantitative sensory testing measures and regional cerebral blood flow measures have been noted to differ from healthy controls in both subjects with fibromyalgia and those with interstitial cystitis when studied independently. The present study examined such measures in subjects with the diagnosis of interstitial cystitis both with and without the co-diagnosis of fibromyalgia to determine whether differences in these measures may be associated with co-morbidity. Female subjects with the diagnosis of interstitial cystitis with ($n = 15$) and without ($n = 19$) the co-diagnosis of fibromyalgia as well as healthy control subjects ($n = 41$) underwent quantitative sensory testing. A subset of these patients (9 with and 9 without fibromyalgia) underwent brain perfusion studies using arterial spin labeled functional magnetic resonance imaging. An analysis was performed of absolute regional cerebral blood flow of regions-of-interest when experiencing a full bladder compared with an empty bladder. Subjects with both interstitial cystitis and fibromyalgia were more hypersensitive than those without fibromyalgia as well as healthy controls in most sensory measures except heat. Subjects with interstitial cystitis, but no fibromyalgia, differed from healthy controls only in toleration of the ischemic forearm task. Other co-morbidities were more common in those subjects with both interstitial cystitis and fibromyalgia. Bladder fullness was associated with significantly greater whole brain gray matter blood flow in subjects with interstitial cystitis and fibromyalgia when compared with that of subjects with interstitial cystitis without fibromyalgia. Examination of regional cerebral blood flow in individual regions-of-interest demonstrated statistically significant differences between the subjects with interstitial cystitis with and those without fibromyalgia bilaterally in the thalamus, amygdala and hippocampus, as well as the right prefrontal cortex and greater responsiveness to changes in bladder fullness in the insula. It was concluded that quantitative sensory testing and brain perfusion data support that there are two phenotypes of interstitial cystitis patients, which can be differentiated by a co-diagnosis of fibromyalgia. This may affect responsiveness to treatment and suggest the utility of stratifying interstitial cystitis patients according to their co-morbidities.

RELIABILITY AND VALIDITY OF PAIN AND URINARY SYMPTOM SEVERITY ASSESSMENT IN UROLOGIC CHRONIC PELVIC PAIN; A MAPP NETWORK ANALYSIS

Bruce D Naliboff, Kenneth Locke Jr, D Schrepf, James W Griffith, Robert Moldwin, John N Krieger, Larissa V Rodriguez, Alisa J Stephens-Shields, J Quentin Clemens, H Henry Lai, Siobhan Sutcliffe, Bayley J Taple, David Williams, Michael A Pontari, Chris Mullins, J Richard Landis, MAPP Research Network. *J Urol.* 2022 Jan 21;101097JU0000000000002438. doi: 10.1097/JU.0000000000002438. Online ahead of print. PMID: 35060778 DOI: 10.1097/JU.0000000000002438

The aim of this MAPP study was to assess reliability and validity of an efficient severity assessment for pelvic pain and urinary symptoms in urologic chronic pelvic pain syndrome (UCPPS), which consists of interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). 578 patients were assessed using brief, empirically derived self-report scales for Pelvic Pain Severity (PPS) and Urinary Symptoms Severity (USS) four times during a one-month period and baseline clinic visit that included urologic, pain and illness-impact measures. Mild, moderate and severe categories on each dimension were examined for measurement stability and construct validity. PPS and USS severity categories had adequate reliability and both discriminant validity (differential relationships with specific clinical and self-report measures) and convergent validity (common association with non-urological somatic symptoms). For example, increasing PPS was associated with pelvic tenderness and widespread pelvic pain, whereas USS was associated with urgency during a bladder filling test and increased sensory sensitivity. PPS and USS categories were independently associated with non-urological pain and emotional distress. A descriptive analysis identified higher likelihood characteristics associated with having moderate to severe PPS or USS or both. Lack of sex interactions indicated that the measures are comparable in IC/BPS and CP/CPPS. It was concluded that women and men with UCPPS can be reliably subgrouped using brief self-report measures of mild, moderate or severe pelvic pain and urinary symptoms. Comparisons with a broad range of clinical variables demonstrate the validity and potential clinical utility of these classifications, including use in clinical trials, health services and biological research.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: BASIC SCIENCE, DIAGNOSIS AND TREATMENT

BIOMARKERS IN THE LIGHT OF THE ETIOPATHOLOGY OF IC/BPS

Jochen Neuhaus, Mandy Berndt-Paetz, Andreas Gonsior. *Diagnostics (Basel)*. 2021 Nov 29;11(12):2231. doi: 10.3390/diagnostics11122231. PMID: 34943467 PMCID: PMC8700473 DOI: 10.3390/diagnostics11122231.

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In this review, the authors from Germany focused on putatively interesting biomarkers of interstitial cystitis/bladder pain syndrome (IC/BPS) in relation to the etiopathology of this disease. Since its etiopathology is still under discussion, the development of novel biomarkers is critical for the correct classification of the patients in order to open personalized treatment options, on the one hand, and to separate true IC/BPS from the numerous confusable diseases with comparable symptom spectra on the other hand. There is growing evidence supporting the notion that the classical or Hunner-type IC (HIC) and the non-Hunner-type IC (NHIC) are different diseases with different etiopathologies and different pathophysiology at the full-blown state. While genetic alterations indicate close relationship to allergic and autoimmune diseases, at present, the genetic origin of IC/BPS could be identified. Disturbed angiogenesis and impairment of the microvessels could be linked to altered humoral signalling cascades leading to enhanced VEGF levels which in turn could enhance leucocyte and mast cell invasion. Recurrent or chronic urinary tract infection has been speculated to promote IC/BPS. New findings show that occult virus infections occurred in most IC/BPS patients and that the urinary microbiome was altered, supporting the hypothesis of infections as major players in IC/BPS. Environmental and nutritional factors may also influence IC/BPS, at least at a late state (e.g., cigarette smoking can enhance IC/BPS symptoms). The damage of the urothelial barrier could possibly be the result of many different causality chains and mark the final state of IC/BPS, the causes of this development having been introduced years ago. The authors conclude that the etiopathology of IC/BPS is complex, involving regulatory mechanisms at various levels. However, using novel molecular biologic techniques promise more sophisticated analysis of this pathophysiological network, resulting in a constantly improvement of our understanding of IC/BPS and related diseases.

BIOMARKERS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME WITH AND WITHOUT HUNNER LESION: A REVIEW AND FUTURE PERSPECTIVES

Yoshiyuki Akiyama. *Diagnostics (Basel)*. 2021 Nov 30;11(12):2238. doi: 10.3390/diagnostics11122238. PMID: 34943475 PMCID: PMC8700457 DOI: 10.3390/diagnostics11122238

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating urinary bladder condition that presents with a wide variety of clinical phenotypes. It is commonly characterized by persistent pelvic pain and lower urinary tract symptoms, such as urinary frequency and urgency. Current clinicopathological and genomic evidence has indicated that IC/BPS with Hunner lesions is a clinically relevant distinct subtype with proven bladder pathology of subepithelial chronic inflammatory changes that are characterized by enhanced local immune responses and epithelial denudation. However, other forms of IC/BPS lacking Hunner lesions are a symptom syndrome complex of non-inflammatory conditions with little evidence of bladder etiology, characterized by aberrant neural activity

in neurotransmission systems which leads to central nervous sensitization with potential involvement of urothelial malfunction, or clinical presentation of somatic and/or psychological symptoms beyond the bladder. Given such distinct potential pathophysiology between IC/BPS subtypes, disease biomarkers of IC/BPS should be provided separately for subtypes with and without Hunner lesions. Tailored approaches that target characteristic immunological inflammatory processes and epithelial denudation for IC/BPS with Hunner lesions, or the sensitized/altered nervous system, urothelial malfunction, association with other functional somatic syndromes, and psychosocial problems for IC/BPS without Hunner lesions, are essential to identify optimal and reliable disease-specific IC/BPS biomarkers.

MRI AS A TOOL TO ASSESS INTERSTITIAL CYSTITIS ASSOCIATED BLADDER AND BRAIN PATHOLOGIES

Rheal A Towner, Nataliya Smith, Debra Saunders, Robert E Hurst. *Diagnostics (Basel)*. 2021 Dec 8;11(12):2298. doi: 10.3390/diagnostics11122298. PMID: 34943535 PMCID: PMC8700450 DOI: 10.3390/diagnostics11122298

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IC/BPS is a chronic, often incapacitating condition characterized by pain seeming to originate in the bladder in conjunction with lower urinary tract symptoms of frequency and urgency and consists of a wide range of clinical phenotypes with diverse etiologies. There are currently no diagnostic tests for IC/BPS. Magnetic resonance imaging (MRI) is a relatively new tool to assess IC/BPS. There are several methodologies that can be applied to assess either bladder wall or brain-associated alterations in tissue morphology and/or pain. IC/BPS is commonly associated with bladder wall hyperpermeability (BWH), particularly in severe cases. This group from the USA developed a contrast-enhanced magnetic resonance imaging (CE-MRI) approach to assess BWH in preclinical models for IC/BPS, as well as for a pilot study for IC/BPS patients. They have also used the CE-MRI approach to assess possible therapies to alleviate the BWH in preclinical models for IC/BPS, which will hopefully pave the way for future clinical trials. In addition, they have used molecular-targeted MRI (mt-MRI) to quantitatively assess BWH biomarkers. Biomarkers, such as claudin-2, may be important to assess and determine the severity of BWH, as well as to assess therapeutic efficacy. Others have also used other MRI approaches to assess the bladder wall structural alterations with diffusion-weighted imaging (DWI), by measuring changes in the apparent diffusion coefficient (ADC), diffusion tensor imaging (DTI), as well as using functional MRI (fMRI) to assess pain and morphological MRI or DWI to assess anatomical or structural changes in the brains of patients with IC/BPS. It would be beneficial if MRI-based diagnostic tests could be routinely used for these patients and possibly used to assess potential therapeutics.

A NOMOGRAM FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS BASED ON NETRIN-1

Xiaojie Ang, Yufeng Jiang, Zongqiang Cai, Qi Zhou, Miao Li, Bin Zhang, Weiguo Chen, Li-Hua Chen, Xi Zhang. *Int Urol Nephrol*. 2021 Dec 13. doi: 10.1007/s11255-021-03084-2. Online ahead of print. PMID: 34897588 DOI: 10.1007/s11255-021-03084-2

This study from China aimed to combine plasma netrin-1 and clinical parameters to construct a diagnostic model for BPS/IC. The authors analyzed the independent diagnostic value of netrin-1 and the correlation with clinical symptom scores of BPS/IC. Clinical parameters were selected using LASSO regression, and a multivariate logistic regression model based on netrin-1 was established, and then a nomogram of BPS/IC prevalence was constructed. The nomogram was evaluated using calibration curves, the C-index, and decision curve analysis (DCA). Finally, the model was validated using an internal validation method. The area under the curve for the ability of netrin-1 to independently predict BPS/IC diagnosis was 0.858, with a sensitivity of 85% and specificity of 82%. The predicted nomogram included three variables: age, CD3 + /CD4 + T lymphocyte ratio, and netrin-1. The C-index of this nomogram was 0.882, and the predicted values were highly consistent with the actual results in the calibration curve. In addition, the internally validated C-index of 0.870 confirms the high reliability of the model. DCA results show that the net patient benefit of the netrin-1 combined with other clinical parameters was higher than that of the single netrin-1 model. It was concluded that netrin-1 can be used as a diagnostic marker for BPS/IC and is associated with pain. The nomogram constructed by combining netrin-1 and clinical parameters was able to predict BPS/IC with great accuracy. In addition, Netrin-1 may also serve as a novel therapeutic target for BPS/IC.

UNSUPERVISED MACHINE LEARNING APPROACHES REVEAL DISTINCT PHENOTYPES OF PERCEIVED BLADDER PAIN: A PILOT STUDY

Patricia J Mwesigwa, Nicholas J Jackson, Ashley T Caron, Falisha Kanji, James E Ackerman, Jessica R Webb, Victoria C S Scott, Karyn S Eilber, David M Underhill, Jennifer T Anger, A Lenore Ackerman. *Front Pain Res*

(Lausanne). 2021 Nov;2:757878. doi: 10.3389/fpain.2021.757878. Epub 2021 Nov 5. PMID: 35036991 PMCID: PMC8758057 DOI: 10.3389/fpain.2021.757878

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IC/BPS is defined as an unpleasant sensation perceived to be related to the bladder with associated urinary symptoms. Due to difficulties discriminating pelvic visceral sensation, IC/BPS likely represents multiple phenotypes with different etiologies that present with overlapping symptomatic manifestations, which complicates clinical management. The authors from the USA hypothesized that unique bladder pain phenotypes or "symptomatic clusters" would be identifiable using machine learning analysis (unsupervised clustering) of validated patient-reported urinary and pain measures. Patients (n = 145) with pelvic pain/discomfort perceived to originate in the bladder and lower urinary tract symptoms answered validated questionnaires [OAB Questionnaire (OAB-q), O'Leary-Sant Indices (ICSI/ICPI), female Genitourinary Pain Index (fGUPI), and Pelvic Floor Disability Index (PFDI)]. In comparison to asymptomatic controls (n = 69), machine learning revealed three bladder pain phenotypes with unique, salient features. The first group chiefly describes urinary frequency and pain with the voiding cycle, in which bladder filling causes pain relieved by bladder emptying. The second group has fluctuating pelvic discomfort and straining to void, urinary frequency and urgency without incontinence, and a sensation of incomplete emptying without urinary retention. Pain in the third group was not associated with voiding, instead being more constant and focused on the urethra and vagina. While not utilized as a feature for clustering, subjects in the second and third groups were significantly younger than subjects in the first group and controls without pain. These phenotypes defined more homogeneous patient subgroups which responded to different therapies on chart review. Current approaches to the management of heterogeneous populations of bladder pain patients are often ineffective, discouraging both patients and providers. The granularity of individual phenotypes provided by unsupervised clustering approaches can be exploited to help objectively define more homogeneous patient subgroups. Better differentiation of unique phenotypes within the larger group of pelvic pain patients is needed to move toward improvements in care and a better understanding of the etiologies of these painful symptoms.

[LOW-PRESSURE HYDRODISTENSION INDUCES BLADDER GLOMERULATIONS IN FEMALE PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Lin-Nei Hsu, Yuh-Shyan Tsai, Yat-Ching Tong. *Neurourol Urodyn.* 2021 Oct 11. doi: 10.1002/nau.24818. Online ahead of print. PMID: 34633704 DOI: 10.1002/nau.24818

The role of hydrodistension in the diagnosis of IC/BPS is controversial. This study from Taiwan evaluated the effect of low-pressure hydrodistension on glomerulation formation in female patients diagnosed with the disease. 60 female patients with the clinical diagnosis of IC/BPS and 30 female controls without the disease underwent cystoscopy and hydrodistension. Cold-cup biopsy was taken from bladder posterior wall at sites with normal cystoscopic appearance before hydrodistension in the IC/BPS group. The tissue samples were processed for histology study. Low-pressure (40 cmH₂O) hydrodistension for 2 min was performed and the appearance of glomerulations was compared between the two groups. High-pressure (80 cmH₂O) hydrodistension for 8 min was then performed as a therapeutic measure for the IC/BPS patients. Further changes to the degree of glomerulations were recorded. Histology showed pathological changes in the normal-appearing IC/BPS bladder mucosa including urothelium denudation, inflammatory cell infiltration, stromal edema, fibrosis, and vascular congestion. Low-pressure hydrodistension induced significant glomerulation formation in the patient group (percentage of patients with Grades 0-4: 0%, 8.3%, 40%, 35%, 10%, respectively) while none in the controls. High-pressure hydrodistension further increased the glomerulation grading in the IC/BPS patients. Structural changes are present in prehydrodistension IC/BPS bladder wall, which may not be macroscopically detectable. Hydrodistension at low pressure is adequate to disrupt the integrity of such diseased mucosa and offers a more discriminative test in the diagnosis of IC/BPS.

[NOTCH1 SIGNALING CONTRIBUTES TO MECHANICAL ALLODYNIA ASSOCIATED WITH CYCLOPHOSPHAMIDE-INDUCED CYSTITIS BY PROMOTING MICROGLIA ACTIVATION AND NEUROINFLAMMATION](#)

Jialiang Chen, Honglu Ding, Bolong Liu, Xiangfu Zhou, Xin Zhou, Zhijun Lin, Fei Yang, Hailun Zhan, Hengjun Xiao. *Mediators Inflamm.* 2021 Oct 4;2021:1791222. doi: 10.1155/2021/1791222. eCollection 2021. PMID: 34646085 PMCID: PMC8505104 DOI: 10.1155/2021/1791222

Notch1 signalling regulates microglia activation, which promotes neuroinflammation. Neuroinflammation plays an essential role in various kinds of pain sensation, including bladder-related pain in bladder pain syndrome/interstitial cystitis (BPS/IC). However, the impact of Notch1 signalling on mechanical allodynia in cyclophosphamide- (CYP-) induced cystitis is unclear. This study from Guangzhou in China is aimed at determining whether and how Notch1 signalling modulates mechanical allodynia of CYP-induced cystitis. CYP

was peritoneally injected to establish a bladder pain syndrome/interstitial cystitis (BPS/IC) rat model. A γ -secretase inhibitor, DAPT, was intrathecally injected to modulate Notch1 signalling indirectly. Mechanical withdrawal threshold in the lower abdomen was measured with von Frey filaments using the up-down method. The expression of Notch1 signalling, Iba-1, OX-42, TNF- α , and IL-1 β in the L6-S1 spinal dorsal horn (SDH) was measured with Western blotting analysis and immunofluorescence staining. Notch1 and Notch intracellular domain (NICD) were both upregulated in the SDH of the cystitis group. Moreover, the expression of Notch1 and NICD was negatively correlated with the mechanical withdrawal threshold of the cystitis rats. Furthermore, treatment with DAPT attenuated mechanical allodynia in CYP-induced cystitis and inhibited microglia activation, leading to decreased production of TNF- α and IL-1 β . Notch1 signalling contributes to mechanical allodynia associated with CYP-induced cystitis by promoting microglia activation and neuroinflammation. This study indicates that inhibition of Notch1 signalling might have therapeutic value for treating pain symptoms in BPS/IC.

INTEGRATED MRNA-MIRNA TRANSCRIPTOME ANALYSIS OF BLADDER BIOPSIES FROM PATIENTS WITH BLADDER PAIN SYNDROME IDENTIFIES SIGNALING ALTERATIONS CONTRIBUTING TO THE DISEASE PATHOGENESIS

Ali Hashemi Gheinani, Akshay Akshay, Mustafa Besic, Annette Kuhn, Irene Keller, Rémy Bruggmann, Hubert Rehrauer, Rosalyn M Adam, Fiona C Burkhard, Katia Monastyrskaya. BMC Urol. 2021 Dec 7;21(1):172. doi: 10.1186/s12894-021-00934-0. PMID: 34876093 PMCID: PMC8653529 DOI: 10.1186/s12894-021-00934-0

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Interstitial cystitis, or bladder pain syndrome (IC/BPS), is a chronic bladder disorder characterized by lower abdominal pain associated with the urinary bladder and accompanied by urinary frequency and urgency in the absence of identifiable causes. IC/PBS can be separated into the classic Hunner's ulcerative type and the more prevalent non-ulcerative disease. The aim of this study from Switzerland and the USA was to unravel the biological processes and dysregulated cell signalling pathways leading to the bladder remodelling in non-ulcerative bladder pain syndrome (BPS) by studying the gene expression changes in the patients' biopsies. The 4 authors performed paired microRNA (miRNA) and mRNA expression profiling in the bladder biopsies of BPS patients with non-Hunner interstitial cystitis phenotype, using comprehensive Next-generation sequencing (NGS) and studied the activated pathways and altered biological processes based on the global gene expression changes. Paired mRNA-miRNA transcriptome analysis delineated the regulatory role of the dysregulated miRNAs by identifying their targets in the disease-induced pathways. EIF2 Signalling and Regulation of eIF4 and p70S6K Signalling, activated in response to cellular stress, were among the most significantly regulated processes during BPS. Leukotriene Biosynthesis nociceptive pathway, important in inflammatory diseases and neuropathic pain, was also significantly activated. The biological processes identified using Gene Ontology over-representation analysis were clustered into six main functional groups: cell cycle regulation, chemotaxis of immune cells, muscle development, muscle contraction, remodelling of extracellular matrix and peripheral nervous system organization and development. Compared to the Hunner's ulcerative type IC, activation of the immune pathways was modest in non-ulcerative BPS, limited to neutrophil chemotaxis and IFN- γ -mediated signalling. They identified 62 miRNAs, regulated and abundant in BPS and show that they target the mRNAs implicated in eIF2 signalling pathway. The bladders of non-ulcerative BPS patients recruited in this study had alterations consistent with a strong cell proliferative response and an up-regulation of smooth muscle contractility, while the contribution of inflammatory processes was modest. Pathway analysis of the integrated mRNA-miRNA NGS dataset pinpointed important regulatory miRNAs whose dysregulation might contribute to the pathogenesis. Observed molecular changes in the peripheral nervous system organization and development indicate the potential role of local bladder innervation in the pain perceived in this type of BPS.

A NOVEL INTRAVESICAL DEXTROSE INJECTION IMPROVES LOWER URINARY TRACT SYMPTOMS ON INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Chin-Li Chen, Chien-Chang Kao, Ming-Hsin Yang, Gang-Yi Fan, Juin-Hong Cherng, Chih-Wei Tsao, Sheng-Tang Wu, Tai-Lung Cha, En Meng. Front Pharmacol. 2021 Dec 15;12:755615. doi: 10.3389/fphar.2021.755615. eCollection 2021. PMID: 34975473 PMCID: PMC8715092 DOI: 10.3389/fphar.2021.755615

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IC/BPS is a painful recurrent condition characterized by the discomfort of the bladder, and current treatment options have limited effectiveness. Prolotherapy is a well-known treatment that involves the injection of non-biologic solutions to reduce pain and/or promote proliferation of soft tissue, and dextrose is the most common injectate. This study from Taiwan investigated the effects of dextrose prolotherapy in a rat model of IC/BPS and patients with IC/BPS. Cyclophosphamide was used to induce IC/BPS in rats, and intravesical instillation of 10% dextrose solution was performed. After 1 week, the authors conducted a urodynamic test, bladder staining, and

ECM-related gene expression analysis to examine the treatment's efficacy. The results demonstrated that dextrose prolotherapy in patients with IC/BPS reduced the frequency of treatment over time, with the mean number of treatments being 3.03 ± 1.52 , and significantly reduced the incidence of nocturia and questionnaire scores associated with symptoms. Dextrose prolotherapy significantly enhanced EGF level and, in contrast, reduced the level of HGF, PIGF-1, and VEGF-D after several weeks following treatment. The cytokine analysis showed that the expressions of IL-12p70 and IL-10 were significantly up-regulated after dextrose prolotherapy in IC/BPS patients. The levels of most growth factors and cytokines in IC/BPS patients had no significant difference and showed a similar tendency as time progressed when compared to healthy controls. Overall, the alteration of growth factors and cytokines exhibited safe treatment and potential stimulation of tissue remodelling. In summary, the authors report that their study demonstrated that dextrose prolotherapy is a promising treatment strategy for IC/BPS disease management.

[DAILY LOW DOSE OF TADALAFIL IMPROVES PAIN AND FREQUENCY IN BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS PATIENTS.](#)

Abreu-Mendes P, Dias N, Simaes J, Dinis P, Cruz F, Pinto R. Turk J Urol. 2022; 48(1): 82-87. DOI: 10.5152/tud.2022.21292.

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BPS/IC is a chronic disease, with consequent high morbidity. Increasing evidence suggests that bladder afferent hyperexcitability, through neurogenic bladder inflammation and urothelial dysfunction, plays a key role in the pathophysiology of BPS/IC. The rationale of using phosphodiesterase type 5 inhibitors (PDE5i) would be to decrease bladder afferent hyperactivity. Detrusor relaxation, improvement of microcirculation, and a decrease in adrenergic nociceptive overactivity would be other effects in bladder tissue. The authors from Portugal aimed to evaluate the efficacy, tolerability, and safety of a daily low dose of 5mg tadalafil in refractory BPS/IC patients. A total of 14 refractory BPS/IC female patients, previously evaluated with a physical examination, bladder diary, bladder-pain related visual analogue score, O'Leary-Sant Scores (OSS) for symptoms and problems, and quality of life (QoL) question from International Prostate Symptom Score, were treated with 5mg of tadalafil, for 3months. Re-evaluations occurred at 4 and 12weeks. Adverse events were assessed and recorded. Urinary frequency, OSS, and QoL were significantly improved at 1-month follow-up (10 6 2.5, 21.9 6 4.1, and 4 6 1.5, respectively, $P < .05$). Pain intensity and volume voided were significantly improved at a 3-month follow-up (3.5 6 2 and 266.7 6 60.5, $P < .05$). Patients referred to urinary frequency as the most important parameter improved at 4weeks, and pain at 3months. No differences between ulcerated and nonulcerated patients were observed. Two patients dropped out due to unsatisfactory results and two due to persistent headache and/or tachycardia, but both events were resolved after discontinuing the drug. It was concluded that daily low-dose tadalafil is an easy, well-tolerated, and effective treatment for refractory BPS/IC in women.

[REAL WORLD USE OF ORAL TREATMENTS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IN THE UK: OUTCOME OF A CROSS SECTIONAL STUDY](#)

Kamaluddeen Garba, Miriam Avery, Muhammadbukhoree Yusuh, Omar Abdelwahab, Scott Harris, Brian R Birch, Bashir A Lwaleed. Neurourol Urodyn. 2021 Nov 29. doi: 10.1002/nau.24840. Online ahead of print. PMID: 34843134 DOI: 10.1002/nau.24840

The purpose of this study was to describe the oral treatments people living with IC/BPS are using to treat their urologic condition in the UK. A questionnaire hyperlink encompassing current and previous medications taken for IC/BPS with other sociodemographic and diagnostic indices was available to the Bladder Health UK website. Interested and fully consented individuals accessed and completed the survey. A total of 601 accessed the questionnaire of whom 173 participants responded (response rate: 28.7%) with a mean \pm SD O'Leary/Sant scores of 20.12 ± 9.38 . A sample size of 171 was estimated to be used in the survey. A fifth of the participants were not on any treatment at all. Amitriptyline was the most prevalent medication in use both alone and in combination. A shift in the use of unapproved (for IC/BPS) antidepressant, smooth muscle relaxant, opioids, gabapentinoids, and antibiotics was observed in the sample. There were no significant differences between the mean (SD) O'Leary/Sant scores of cohorts currently taking oral medications and those not taking it. More than two-thirds of the participants had been diagnosed with the disease more than 5 years. Just under a half (47.4%) of participants reported a history of allergy. The authors conclude that their study provides contemporary evidence that the treatments used for managing IC/BPS encompass a broad range of medications both recommended and not recommended by current guidelines. The latter suggests patients are willing to try novel treatments when more conventional ones are ineffective.

AN INDIRECT COMPARISON META-ANALYSIS OF NONINVASIVE INTRAVESICAL INSTILLATION AND INTRAVESICAL INJECTION OF BOTULINUM TOXIN-A IN BLADDER DISORDERS

Gao Yunfeng, Lai Fei, Liu Junbo, Yang Dingyuan, Huang Chaoyou. *Int Urol Nephrol*. 2022 Jan 19. doi: 10.1007/s11255-022-03107-6. Online ahead of print.

Botulinum toxin type A (BTX-A) intravesical instillation and BTX-A intravesical injection are both effective treatments for overactive bladder (OAB) and interstitial cystitis/bladder pain syndrome (IC/BPS), but direct comparative studies of the two treatments are lacking. The authors from China conducted a pairs-comparison meta-analysis and an adjusted indirect comparison meta-analysis extracting published data from randomized controlled trials in literature databases from the inception of each database to Aug. 31, 2021, evaluating efficacy and safety of BTX-A intravesical instillation and BTX-A intravesical injection. They also carried out a subgroup analysis. They identified 24 trials in 21 studies were included in their study, of which 18 trials in 17 studies were BTX-A intravesical injections, 6 trials in 4 studies were BTX-A intravesical instillation. Compared with the normal saline injection, BTX-A intravesical injections for patients with OAB and IC/ BPS can obviously improve the symptoms of urinary frequency, urgency episode, UI and UUI, but BTX-A significantly increased the rate of urinary retention and urinary tract infection and increased PVR. Adjusted indirect comparison meta-analysis showed that BTX-A intravesical injections was more effective than BTX-A intravesical instillation. Surprisingly, BTX-A intravesical instillation had fewer side effects than BTX-A intravesical injections. Although BTX-A intravesical injections for OAB and IC/BPS have been significantly superior to BTX-A intravesical instillation, it has major side effects, but this needs to be confirmed by more large-scale, multicenter, direct comparison randomized controlled trials.

BOTULINUM TOXIN-A INJECTION IN CHRONIC PELVIC PAIN SYNDROME TREATMENT: A SYSTEMATIC REVIEW AND POOLED META-ANALYSIS

Andrea Panunzio, Alessandro Tafuri, Giovanni Mazzucato, Clara Cerrato, Rossella Orlando, Vincenzo Pagliarulo, Alessandro Antonelli, Maria Angela Cerruto. *Toxins (Basel)*. 2022 Jan 1;14(1):25. doi: 10.3390/toxins14010025. PMID: 35051002 PMCID: PMC8780260 DOI: 10.3390/toxins14010025

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Pain management of patients with chronic pelvic pain syndrome (CPPS) is challenging, because pain is often refractory to conventional treatments. Botulinum toxin A (BTX-A) may represent a promising therapeutic strategy for these patients. The aim of this systematic review was to investigate the role of BTX-A in CPPS treatment. The authors from Italy reviewed the literature for prospective studies evaluating the use of BTX-A in the treatment of CPPS. After screening 1001 records, 18 full-text manuscripts were selected, comprising 13 randomized clinical trials and five comparative studies. They covered overall 896 patients of both sexes and several subtype of CPPS (interstitial cystitis/bladder pain syndrome, chronic prostatitis/prostate pain syndrome, chronic scrotal pain, gynecological pelvic pain, myofascial pelvic pain). The clinical and methodological heterogeneity of studies included makes it difficult to do an overall estimation of the real effect of BTX-A on pain and other functional outcomes of various CPPS subtypes. However, considering pooled meta-analysis results, a benefit in pain relief was showed for BTX-A-treated patients both in the overall studies populations and in the overall cohorts of patients with CPP due to bladder, prostate, and gynecological origin. It was concluded that BTX-A could be an efficacious treatment for some specific CPPS subtypes. Higher level studies are needed to assess the efficacy and safety of BTX-A and provide objective indications for its use in CPPS management.

THE IMPACT OF ORTHOTOPIC RECONSTRUCTION ON FEMALE SEXUALITY AND QUALITY OF LIFE AFTER RADICAL CYSTECTOMY FOR NON-MALIGNANT BLADDER CONDITIONS

Chiara Borghi, Margherita Manservigi, Elena Sofia Milandri, Carmelo Ippolito, Pantaleo Greco, Lucio Dell'Atti. *Arch Ital Urol Androl*. 2021 Sep 30;93(3):255-261. doi: 10.4081/aiua.2021.3.255. PMID: 34839630 DOI: 10.4081/aiua.2021.3.255

The purpose of this study was to review the literature on the impact on female quality of life and sexual function of orthotopic reconstruction after radical cystectomy for non-malignant bladder conditions. Radical cystectomy is commonly required to treat malignant conditions but may also be considered for the treatment of non-malignant diseases. These heterogeneous group of disorders includes interstitial cystitis, painful bladder syndrome, neurogenic bladder, haemorrhagic/ radiation cystitis, endometriosis and refractory genitourinary fistula. Treatment begins with non-invasive medical therapies but, in non-responder cases, a surgical solution should be considered. Such invasive techniques include urinary diversion and reconstructive procedures that have an impact on health-related quality of life, physical, social, and mental status. In comparison to other reconstructive options, orthotopic neobladder allows the restoration of a normal self-image and consequently it is the most suitable procedure when a surgical reconstruction is necessary for non-malignant conditions.

However, women can face many disorders that impact on everyday life, such as voiding dysfunction or sexual activity problems. Scant data are available about quality of life, sexual life and self-perception in women treated by cystectomy for benign conditions and most literature is dedicated to those indicators in cancer patients. More research is needed to understand the tolerability and the quality of life results of the female population affected by benign conditions undergoing this kind of surgical approach.

[DIAGNOSIS OF INTERSTITIAL CYSTITIS: PRACTICE-ORIENTATED DIAGNOSTIC WORK-UP]

[Article in German]

Antje Foresti, Daniela Schultz-Lampel. Aktuelle Urol. 2021 Nov 3. doi: 10.1055/a-1645-0987. Online ahead of print. PMID: 34734396 DOI: 10.1055/a-1645-0987

Interstitial cystitis is a chronic orphan disease of the urinary bladder characterised by its main symptoms of bladder pain, persistent urge to void and urinary frequency. Due to a variety of confusable diseases and different pathophysiologies, the diagnosis of IC is still a diagnosis of exclusion and remains a challenge for doctors and patients alike. Patients often experience misdiagnosis and unsuccessful treatment for years. Therefore, the primary goal for these patients with chronic pain must be a rapid diagnosis and initiation of adequate treatment. This article focuses on transferring the consensus-based recommendations of the current German S2k guideline "Diagnosis and Treatment of Interstitial Cystitis" (IC/BPS) (2018 AWMF register No.: 043/050) into a practice-orientated and structured diagnostic work-up process.

[REHABILITATION OF PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS)]

[Article in German]

Winfried Vahlensieck, Raschid El Idrissi, Ursula Gerhard-Franke, Maren Huber, Jennifer Jenner, Dirk-Henrik Zermann. Aktuelle Urol. 2021 Oct 20. doi: 10.1055/a-1639-9761. Online ahead of print. PMID: 34670317 DOI: 10.1055/a-1639-9761

After unsuccessful outpatient conservative treatment or invasive inpatient treatment and after cystectomy in interstitial cystitis/bladder pain syndrome (IC/BPS), an inpatient discipline-specific urological rehabilitation (rehab) should be proposed according to the German guideline on IC/BPS. During rehab, diagnostic results will be completed. Multimodal therapy includes the optimisation of lifestyle and medication. Intensive psychotherapy may frequently improve the processing of the disease. Various forms of exercise therapy and physical therapy with water applications, thermotherapy, several forms of massage and electrical or magnetic therapies as well as nutritional advice frequently alleviate complaints in IC/BPS. The different therapies are modified during rehab, if necessary. Social medicine evaluation and advice, e.g. on grade of handicap or ability to work, are also important issues in rehab. Two-thirds of patients show an essential improvement after rehab, which lasts for a prolonged period in about 50% of patients.

[S2K GUIDELINE ON THE DIAGNOSIS AND TREATMENT OF INTERSTITIAL CYSTITIS (IC/BPS) : DISCUSSION OF THE CURRENT GUIDELINE USING A CASE STUDY]

[Article in German]

J Tolle, B T Kaftan, Th Bschiepfer. Urologe A. 2022 Jan 17. doi: 10.1007/s00120-021-01753-9. Online ahead of print. PMID: 35037970 DOI: 10.1007/s00120-021-01753-9

IC/BPS is a chronic progressive disorder that is often difficult and unsatisfactory for the person affected and the treating therapist. Treatment should therefore be comprehensive, interdisciplinary, multimodal and take into account the biopsychosocial model. The guideline forms a thread through the diverse diagnostic and therapeutic options and provides extensive background information on the definition, epidemiology and aetiopathogenesis of this rare disease. However, practice and theory/guideline are different. Adaptation to the individual case is therefore necessary and explicitly desired. The guideline should therefore serve as a source of ideas for colleagues to compile their own standards suitable for their practice. On the one hand, therapy approaches that have been tried and tested in everyday clinical practice are passed on. On the other hand, the frequent lack of evidence should also be viewed critically. Further studies, if possible multi-centre, specifically designed for different aspects of IC/BPS would be desirable. Close networking between therapists in private practice and special centres is essential for the best possible treatment of people with IC/BPS. The guideline is intended to show the limits of what can be done in practices and outpatient clinics and to provide guidance on when patients should be referred to a "Centre for Interstitial Cystitis and Pelvic Pain". Overall, the guideline has improved the presence of this rare disease among colleagues. A comprehensive supplement, update and further substantiation with the state of current research is thus desirable.

[ACTIVATION OF GPR18 BY RESOLVIN D2 RELIEVES PAIN AND IMPROVES BLADDER FUNCTION IN CYCLOPHOSPHAMIDE-INDUCED CYSTITIS THROUGH INHIBITING TRPV1](#)

Qudong Lu, Yang Yang, Hengshuai Zhang, Cheng Chen, Jiang Zhao, Zhenxing Yang, Yi Fan, Longkun Li, Huan Feng, Jingzhen Zhu, Shanhong Yi. Drug Des Devel Ther. 2021 Nov 15;15:4687-4699. doi: 10.2147/DDDT.S329507. eCollection 2021. PMID: 34815664 PMCID: PMC8604640 DOI: 10.2147/DDDT.S329507

Hyperalgesia and bladder overactivity are two main symptoms of interstitial cystitis/bladder pain syndrome (IC/BPS). Cannabinoid receptors participate in the modulation of pain and bladder function. GPR18, a member of the cannabinoid receptor family, also participates in the regulation of pain and bladder function, but its underlying mechanisms are unknown. In this study from Chongqing, China, Lu and colleagues examined the role of GPR18 in IC/BPS. A rat model of IC/BPS was established with cyclophosphamide (CYP). Paw withdrawal threshold (PWT) measurement and cystometry were used to evaluate pain and bladder function, respectively. RT-PCR, Western blotting and immunofluorescence were used to assess the expression and distribution of GPR18. The role of GPR18 in pain and bladder function was studied by intrathecal injection of resolvin D2 (RvD2, a GPR18 agonist) and O-1918 (a GPR18 antagonist). Calcium imaging was used to study the relationship between GPR18 and TRPV1. A rat model of IC/BPS, which exhibited a decreased PWT and micturition interval, was successfully established with CYP. The mRNA and protein expression of GPR18 was reduced in the bladder and dorsal root ganglia (DRG) in rats with CYP-induced cystitis. Intrathecal injection of RvD2 increased the PWT and micturition interval. However, O-1918 blocked the therapeutic effect of RvD2. GPR18 was present in bladder afferent nerves and colocalized with TRPV1 in DRG, and RvD2 decreased capsaicin-induced calcium influx in DRG. Activation of GPR18 by RvD2 alleviated hyperalgesia and improved bladder function, possibly by inhibiting TRPV1 in rats with CYP-induced cystitis.

[USE OF INTRAVESICAL INJECTIONS OF PLATELET-RICH PLASMA FOR THE TREATMENT OF BLADDER PAIN SYNDROME: A COMPREHENSIVE LITERATURE REVIEW](#)

Francesco Trama, Ester Illiano, Alessandro Marchesi, Stefano Brancorsini, Felice Crocetto, Savio Domenico Pandolfo, Alessandro Zucchi, Elisabetta Costantini. Antibiotics (Basel). 2021 Oct 1;10(10):1194. doi: 10.3390/antibiotics10101194. PMID: 34680774 PMCID: PMC8532598 DOI: 10.3390/antibiotics10101194

Bladder pain syndrome/interstitial cystitis (BPS/IC) or primary bladder pain syndrome (PBPS) is a complex and poorly understood condition. This comprehensive review from Italy aimed to discuss the potential application of platelet-rich plasma (PRP) in the treatment of BPS/IC. The pathophysiology of BPS/IC is characterized by urothelial damage that triggers a chain of events leading to chronic inflammation and other conditions. Frequently, in subjects affected by BPS/IC, recurrent urinary tract infection (rUTI) is associated with difficult therapeutic management. For these reasons, many oral and intravesical treatments (e.g., antibiotic therapy and intravesical anesthetic instillations) have been proposed to alleviate the symptoms of IC/BPS. However, the limitation of these treatments is the short duration of improvement. This review analyzes the efficacy of intravesical PRP injections in subjects with BPS/IC and tries to understand the potential therapeutic effects on the pathophysiology of this disease. The authors showed an improvement in the histological pattern with less bleeding in treated subjects, a lower presence of inflammatory cytokines and an increase in the mitotic index of urothelial cells in animals treated with intravesical PRP. In the three prospective clinical trials analyzed, patients with BPS/IC who underwent monthly intravesical PRP injections were found to have a statistically significant improvement in symptoms with modulation of growth factors and inflammatory proteins. New evidence suggests that treatment with intravesical PRP could improve urothelial regeneration and reduce chronic inflammation in BPS/IC, modifying the clinical history of its pathology.

[INTRAVESICAL DRUG DELIVERY APPROACHES FOR IMPROVED THERAPY OF URINARY BLADDER DISEASES](#)

Luca Palugan, Matteo Cerea, Micol Cirilli, Saliha Moutaharrik, Alessandra Maroni, Lucia Zema, Alice Melocchi, Marco Ubaldi, Ilaria Filippin, Anastasia Foppoli, Andrea Gazzaniga. Int J Pharm X. 2021 Oct 23;3:100100. doi: 10.1016/j.ijpx.2021.100100. eCollection 2021 Dec. PMID: 34765967 PMCID: PMC8569723 DOI: 10.1016/j.ijpx.2021.100100

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Diseases of the urinary bladder have high incidence rates and burden healthcare costs. Their pharmacological treatment involves systemic and local drug administration. The latter is generally accomplished through instillation of liquid formulations and requires repeated or long-term catheterization that is associated with discomfort, inflammation and bacterial infections. Consequently, compliance issues and dropouts are frequently reported. Moreover, instilled drugs are progressively diluted as the urine volume increases and rapidly excreted. When penetration of drugs into the bladder wall is needed, the poor permeability of the urothelium has also to be accounted for. Therefore, much research effort is spent to overcome these hurdles, thereby improving the

efficacy of available therapies. Particularly, indwelling delivery systems suited for i) insertion into the bladder through the urethra, ii) intra-organ retention and prolonged release for the desired time lapse, iii) final elimination, either spontaneous or by manual removal, have been proposed to reduce the number of catheterization procedures and reach higher drug levels at the target site. Vesical retention of such devices is allowed by the relevant expansion that can either be triggered from the outside or achieved exploiting elastic and purposely 4D printed shape memory materials. In this article, the main rationales and strategies for improved intravesical delivery are reviewed.

POSSIBLE ASSOCIATION BETWEEN BLADDER WALL MORPHOLOGICAL CHANGES ON COMPUTED TOMOGRAPHY AND BLADDER-CENTERED INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Jia-Fong Jhang, Yung-Hsiang Hsu, Han-Chen Ho, Yuan-Hong Jiang, Cheng-Ling Lee, Wan-Ru Yu, Hann-Chorng Kuo. Biomedicines. 2021 Sep 24;9(10):1306. doi: 10.3390/biomedicines9101306. PMID: 34680422 PMCID: PMC8533058 DOI: 10.3390/biomedicines9101306

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This study from Taiwan aimed to evaluate the clinical significance of urinary bladder wall thickening on computed tomography (CT) among patients with IC/BPS. Patients with IC/BPS were prospectively enrolled and classified into three groups according to bladder CT finding: smooth bladder wall, focal bladder thickening, and diffuse bladder thickening. Among the 100 patients with IC/BPS, 49, 36, and 15 had smooth bladder wall, focal bladder thickening, and diffuse bladder thickening on CT, respectively. Patients with Hunner's lesion showed a higher proportion of diffuse and focal bladder thickening compared to those without the same. Patients with diffuse bladder thickening displayed smaller first sensation of filling, cystometric bladder capacity, and voided volume compared to the rest. Patients with focal and diffuse thickening had a higher proportion of inflammatory cell infiltration, uroepithelial cell denudation, and granulation tissue compared to those with smooth bladder wall. Bladder wall thickening on CT was correlated with clinical phenotypes of IC/BPS, including histopathological findings. Focal or diffuse bladder wall thickening on CT might indicate the presence of chronic bladder wall inflammation and fibrosis and could be used to differentiate bladder-centred IC/BPS.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENT IS ASSOCIATED WITH SUBSEQUENT INCREASED RISKS OF OUTPATIENT VISITS AND HOSPITALIZATIONS: A POPULATION-BASED STUDY

Kun-Lin Hsieh, Hung-Yen Chin, Tsia-Shu Lo, Cheng-Yu Long, Chung-Han Ho, Steven Kuan-Hua Huang, Yao-Chi Chuang, Ming-Ping Wu. PLoS One. 2021 Sep 7;16(9):e0256800. doi: 10.1371/journal.pone.0256800. eCollection 2021. PMID: 34492065 PMCID: PMC8423233 DOI: 10.1371/journal.pone.0256800

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is not only a chronic urinary bladder pain syndrome but is also associated with multifactorial etiology. This study from Taiwan and China aimed to test the hypothesis that IC/BPS is associated with subsequent increased risks of outpatient visits and hospitalizations. Using nationwide database, the diagnoses were based on the International Classification Codes (ICD-9-CM) (595.1) of at least three outpatient services during 2002-2008, (n = 27,990) and cystoscopic finding Hunner type and/or glomerulation with pre-audit criteria. All recruited cases monitored for subsequent outpatient visits and hospitalizations for 2 years, including all-cause and specialty-specific departments, were classified according to medical specialty and age group (<40, 40-60, ≥60 years of age). IC/BPS patients have more overall outpatient department (OPD) visits and an overall adjusted incidence rate ratio (IRR) of 1.64. As for specialty, IRRs were higher in psychiatry (2.75), Chinese medicine (2.01), and emergency medicine (2.00), besides urology and gynecology. The IRRs decreased as age advanced (2.01, 1.71, and 1.44, respectively), except for gynecology (2.42, 2.52, and 2.81). A similar phenomenon happens in hospitalization with IRR of 1.69. Due to claim data characteristics, whether ulcer type IC/BPS findings can be deductive to non-ulcer type remains inclusive. Current results indicate the impacts of healthcare burden in broad spectrum about IC/PBS patients. IC/BPS has been suggested to be associated with lower threshold of healthcare visits and some coexisting disease and is comprised of systemic dysregulation and is beyond the scope of local bladder-urethra disease. Adequate recognition of associated or comorbid factors and possible recommendation or referral for IC/BPS patients can help provide better healthcare quality.

B6 MOUSE STRAIN: THE BEST FIT FOR LPS-INDUCED INTERSTITIAL CYSTITIS MODEL

Ching-Hao Chen, Chun-Hou Liao, Kuo-Chiang Chen, Kuan-Lin Wang, Xiao-Wen Tseng, Wei-Kung Tsai, Han-Sun Chiang, Yi-No Wu. Int J Mol Sci. 2021 Nov 8;22(21):12053. doi: 10.3390/ijms222112053. PMID: 34769483 DOI: 10.3390/ijms222112053

Interstitial cystitis (IC) is a chronic inflammatory disease characterized by bladder pain and increased urinary frequency. Although the C57BL/6J (B6) and FVB/NJ (FVB) mouse strains are commonly used as animal models

for studies involving the urinary system, few reports have compared their lower urinary tract anatomy, despite the importance of such data. This study from Taiwan and the UK aimed to characterize bladder function changes in FVB and B6 mouse strains with lipopolysaccharide (LPS)-induced IC, to understand mouse model-based bladder research. The bladder function parameters were measured by cystometrogram. Histological assay was examined by hematoxylin and eosin stain, Masson's trichrome stain, and immunofluorescence staining. Results indicated that the two strains in the control group exhibited different bladder structures and functions, with significant anatomical differences, including a larger bladder size in the FVB than in the B6 strain. Furthermore, cystometry tests revealed differences in bladder function pressure. LPS-treated B6 mice presented significant changes in peak pressure, with decreased intercontraction intervals; these results were similar to symptoms of IC in humans. Each strain displayed distinct characteristics, emphasizing the care required in choosing the appropriate strain for bladder-model studies. The results suggested that the B6 mouse strain is more suitable for IC models.

URINARY BIOMARKERS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND ITS IMPACT ON THERAPEUTIC OUTCOME

Hung-Yu Lin, Jian-He Lu, Shu-Mien Chuang, Kuang-Shun Chueh, Tai-Jui Juan, Yi-Chang Liu, Yung-Shun Juan. Diagnostics (Basel). 2021 Dec 29;12(1):75. doi: 10.3390/diagnostics12010075. PMID: 35054241 DOI: 10.3390/diagnostics12010075

Interstitial cystitis/bladder pain syndrome (IC/BPS) is defined as a chronic bladder disorder with suprapubic pain (pelvic pain) and pressure and/or discomfort related to bladder filling accompanied by lower urinary tract symptoms, such as urinary frequency and urgency without urinary tract infection (UTI) lasting for at least 6 weeks. IC/BPS presents significant bladder pain and frequency urgency symptoms with unknown etiology, and it is without a widely accepted standard in diagnosis. Patients' pathological features through cystoscopy and histologic features of bladder biopsy determine the presence or absence of Hunner lesions. IC/BPS is categorized into Hunner (ulcerative) type IC/BPS (HIC/BPS) or non-Hunner (nonulcerative) type IC/BPS (NHIC/BPS). The pathophysiology of IC/BPS is composed of multiple possible factors, such as chronic inflammation, autoimmune disorders, neurogenic hyperactivity, urothelial defects, abnormal angiogenesis, oxidative stress, and exogenous urine substances, which play a crucial role in the pathophysiology of IC/BPS. Abnormal expressions of several urine and serum specimens, including growth factor, methylhistamine, glycoprotein, chemokine and cytokines, might be useful as biomarkers for IC/BPS diagnosis. Further studies to identify the key molecules in IC/BPS will help to improve the efficacy of treatment and identify biomarkers of the disease. In this review from Taiwan, the authors discuss the potential medical therapy and assessment of therapeutic outcome with urinary biomarkers for IC/BPS.

POSSIBLE ROLE OF INTRAVENOUS ADMINISTRATION OF MESENCHYMAL STEM CELLS TO ALLEVIATE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IN A TOLL-LIKE RECEPTOR-7 AGONIST-INDUCED EXPERIMENTAL ANIMAL MODEL IN RAT

Hidetoshi Tabata, Masanori Sasaki, Yuko Kataoka-Sasaki, Nobuo Shinkai, Koji Ichihara, Naoya Masumori, Jeffery D Kocsis, Osamu Honmou. BMC Urol. 2021 Nov 13;21(1):156. doi: 10.1186/s12894-021-00923-3. PMID: 34774029 DOI: 10.1186/s12894-021-00923-3

IC/BPS categorized with and without Hunner lesions is a condition that displays chronic pelvic pain related to the bladder with no efficacious treatment options. There are strong associations suggested between Hunner-type IC and autoimmune diseases. Recently, the authors from Japan established an animal model of Hunner-type IC using a Toll-like receptor-7 (TLR7) agonist. Intravenous infusion of mesenchymal stem cells (MSCs) can be used to treat injury via multimodal and orchestrated therapeutic mechanisms including anti-inflammatory effects. Here, they investigated whether infused MSCs elicit therapeutic efficacy associated with the TLR7-related anti-inflammatory pathway in their Hunner-type IC model. Voiding behaviors were monitored 24 h prior to the Loxoribine (LX), which is a TLR7 agonist instillation in order to establish a Hunner-type IC model (from -24 to 0 h) in female Sprague-Dawley rats. LX was instilled transurethrally into the bladder. At 0 h, the initial freezing behavior test confirmed that no freezing behavior was observed in any of the animals. The LX-instilled animals were randomized. Randomized LX-instilled rats were intravenously infused with MSCs or with vehicle through the right external jugular vein. Sampling tissue for green fluorescent protein (GFP)-positive MSCs were carried out at 48 h. Second voiding behavior tests were monitored from 72 to 96 h. After the final evaluation of the freezing behavior test at 96 h after LX instillation (72 h after MSC or vehicle infusion), histological evaluation with H&E staining and quantitative real-time polymerase chain reaction (RT-PCR) to analyze the mRNA expression levels of inflammatory cytokines were performed. Freezing behavior was reduced in the MSC group, and voiding behavior in the MSC group did not deteriorate. Hematoxylin-eosin staining showed that mucosal

edema, leukocyte infiltration, and hemorrhage were suppressed in the MSC group. The relative expression of interferon- β mRNA in the bladder of the MSC group was inhibited. Numerous GFP-positive MSCs were distributed mainly in the submucosal and mucosal layers of the inflammatory bladder wall. Intravenous infusion of MSCs may have therapeutic efficacy in a LX-instilled Hunner-type IC rat model via a TLR7-related anti-inflammatory pathway.

[A H₂O₂-ACTIVATABLE NANOPROBE FOR DIAGNOSING INTERSTITIAL CYSTITIS AND LIVER ISCHEMIA-REPERFUSION INJURY VIA MULTISPECTRAL OPTOACOUSTIC TOMOGRAPHY AND NIR-II FLUORESCENT IMAGING](#)

Junjie Chen, Longqi Chen, Yinglong Wu, Yichang Fang, Fang Zeng, Shuizhu Wu, Yanli Zhao. Nat Commun. 2021 Nov 25;12(1):6870. doi: 10.1038/s41467-021-27233-4. PMID: 34824274 DOI: 10.1038/s41467-021-27233-4

Developing high-quality NIR-II fluorophores (emission in 1000-1700 nm) for in vivo imaging is of great significance. Benzothiadiazole-core fluorophores are an important class of NIR-II dyes, yet ongoing limitations such as aggregation-caused quenching in aqueous milieu and non-activatable response are still major obstacles for their biological applications. Here, the authors from China and Singapore devise an activatable nanoprobe to address these limitations. A molecular probe named BTPE-NO₂ is synthesized by linking a benzothiadiazole core with two tetraphenylene groups serving as hydrophobic molecular rotors, followed by incorporating two nitrophenyloxoacetamide units at both ends of the core as recognition moieties and fluorescence quenchers. An FDA-approved amphiphilic polymer Pluronic F127 is then employed to encapsulate the molecular BTPE-NO₂ to render the nanoprobe BTPE-NO₂@F127. The pathological levels of H₂O₂ in the disease sites cleave the nitrophenyloxoacetamide groups and activate the probe, thereby generating strong fluorescent emission (950~1200 nm) and ultrasound signal for multi-mode imaging of inflammatory diseases. The nanoprobe can therefore function as a robust tool for detecting and imaging the disease sites with NIR-II fluorescent and multispectral optoacoustic tomography (MSOT) imaging. Moreover, the three-dimensional MSOT images can be obtained for visualizing and locating the disease foci.

[TRIGONE AS A DIAGNOSTIC AND THERAPEUTIC TARGET FOR BLADDER-CENTRIC INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Amy D Dobberfuhr, Stefanie van Uem, Eboo Versi. Int Urogynecol J. 2021 Dec;32(12):3105-3111. doi: 10.1007/s00192-021-04878-9. Epub 2021 Jun 22. PMID: 34156506 DOI: 10.1007/s00192-021-04878-9

The pathophysiology of IC/BPS may be bladder-centric, with afferent nerve hyperexcitability and/or due to neural central sensitization. In bladder-centric disease, the trigone's unmyelinated nociceptive C-fibers are thought to be upregulated, suggesting this as a potential target for diagnostic modalities and for treatment with local anesthetics and chemodenervation. The authors propose that the transvaginal trigone treatment (T3) route of administration of such treatments should be considered in women with IC/BPS, as this approach is easier and less invasive than cystoscopy. For T3, or other bladder-centric treatments to be successful, patient selection should attempt to exclude patients with predominantly neural central sensitization.

[ROLE OF SURGERY IN BLADDER PAIN SYNDROME](#)

Alsulaiman OA, Saad S, Osman NI, Chapple CR. Curr Bladder Dysfunct Rep 16, 87–96 (2021). <https://doi.org/10.1007/s11884-021-00636-1>

Bladder pain syndrome is a clinical condition with many aspects to its presentation and numerous suggested treatments, many of which remain controversial. Reconstructive surgery should only be considered when all the conservative options have been exhausted and only after careful counselling. The purpose of this review is to demonstrate the current evidence in the surgical management of this disease, preparatory to which the authors have reviewed the surgical aspects. For medical treatment, the evidence base is of poor quality and based on case series. Nevertheless, in carefully selected patients after appropriate counselling, excellent results can be achieved both with total cystectomy and augmentation cystoplasty or a continent or incontinent diversion. The authors reviewed the various success rates of the treatments which are described. A multidisciplinary approach is essential to a successful outcome, and it is essential to consider not only the urological, but also broader medical and psychological consequences seen with bladder pain syndrome. Further research should focus on clearly categorizing the patients with well-defined clinical criteria to provide high-quality evidence to support the selection of the most effective treatment.

[INTRAVITAL IMAGING AND SINGLE CELL TRANSCRIPTOMIC ANALYSIS FOR ENGRAFTMENT OF MESENCHYMAL STEM CELLS IN AN ANIMAL MODEL OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Hwan Yeul Yu, Seungun Lee, Hyein Ju, Youngkyu Kim, Jung-Hyun Shin, HongDuck Yun, Chae-Min Ryu, Jinbeom Heo, Jisun Lim, Sujin Song, Sanghwa Lee, Ki-Sung Hong, Hyung-Min Chung, Jun Ki Kim, Myung-Soo Choo, Dong-Myung Shin. *Biomaterials*. 2021 Nov 27;280:121277. doi: 10.1016/j.biomaterials.2021.121277. Online ahead of print. PMID: 34861510 DOI: 10.1016/j.biomaterials.2021.121277

Mesenchymal stem cell (MSC) therapy is a promising treatment for various intractable disorders including IC/BPS. However, an analysis of fundamental characteristics driving in vivo behaviors of transplanted cells has not been performed, causing debates about rational use and efficacy of MSC therapy. In this study from Korea, the authors implemented two-photon intravital imaging and single cell transcriptome analysis to evaluate the in vivo behaviors of engrafted multipotent MSCs (M-MSCs) derived from human embryonic stem cells (hESCs) in an acute IC/BPS animal model. Two-photon imaging analysis was performed to visualize the dynamic association between engrafted M-MSCs and bladder vasculature within live animals until 28 days after transplantation, demonstrating the progressive integration of transplanted M-MSCs into a perivascular-like structure. Single cell transcriptome analysis was performed in highly purified engrafted cells after a dual MACS-FACS sorting procedure and revealed expression changes in various pathways relating to pericyte cell adhesion and cellular stress. Particularly, FOS and cyclin dependent kinase-1 (CDK1) played a key role in modulating the migration, engraftment, and anti-inflammatory functions of M-MSCs, which determined their in vivo therapeutic potency. Collectively, this approach provides an overview of engrafted M-MSC behavior in vivo, which will advance our understanding of MSC therapeutic applications, efficacy, and safety.

[EFFICACY OF PERCUTANEOUS AND TRANSCUTANEOUS POSTERIOR TIBIAL NERVE STIMULATION ON IDIOPATHIC OVERACTIVE BLADDER AND INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS](#)

Amirhossein Ghavidel-Sardsahra, Morteza Ghोजazadeh, Mohammad Sajjad Rahnama'i, Amirreza Naseri, Shahabodin Yazdandoost, Taha Khezerloo, Sepideh Seyedi-Sahebari, Hossein Hosseini-fard, Nafiseh Vahed, Hadi Mostafaei, Hanieh Salehi-Pourmehr, Sakineh Hajebrahimi. *Neurourol Urodyn*. 2022 Jan 15. doi: 10.1002/nau.24864. Online ahead of print. PMID: 35032328 DOI: 10.1002/nau.24864

Percutaneous and transcutaneous posterior tibial nerve stimulation (PTNS and TTNS) showed a promising effect on overactive bladder (OAB) and interstitial cystitis/painful bladder syndrome. This study from Iran, Germany and Austria aimed to give a systematic review and meta-analysis on the efficacy and safety of these therapeutic methods as well. The authors searched studies available on PubMed, Embase, Cochrane, Scopus, Web of Science, and ProQuest on March 31, 2021, to find both published and unpublished studies. Of the total 3194 publications, 68 studies were included in our qualitative evaluation and 9 studies (11 trials) in the quantitative stage. When TTNS or PTNS were compared to sham, placebo, no treatment, or conservative management, a decrease in frequency of urination was observed in both TTNS and PTNS and overall TTNS or PTNS. Significant improvements in mean voiding volume (MVV) and decreasing nocturia were also observed. It was concluded that nerve stimulations, either PTNS or TTNS, appear to be effective interventions in treating refractory idiopathic OAB in terms of daily voiding frequency, MVV, urgency episodes, and nighttime voiding frequency. However, their result did not show any improvement in terms of urinary incontinence, postvoid residual volume or urge incontinence, and maximum cystometric capacity which emphasized the efficacy of these modalities on dry-OAB rather than wet-OAB.

[INHIBITION OF CXCR4 IN SPINAL CORD AND DRG WITH AMD3100 ATTENUATES COLON-BLADDER CROSS-ORGAN SENSITIZATION](#)

Hengshuai Zhang, Xingyou Dong, Zhenxing Yang, Jiang Zhao, Qudong Lu, Jingzhen Zhu, Longkun Li, Shan hong Yi, Jie Xu. *Drug Des Devel Ther*. 2022 Jan 6;16:67-81. doi: 10.2147/DDDT.S336242. eCollection 2022. PMID: 35023903 PMCID: PMC8747645 DOI: 10.2147/DDDT.S336242

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Cross-sensitization of pelvic organs is one theory for why symptoms of gut sickness and interstitial cystitis/bladder pain syndrome overlap. Experimental colitis has been shown to trigger bladder hyperactivity and hyperalgesia in rats. The chemokine receptor CXCR4 plays a key role in bladder function and central sensitization. The authors from China aimed to study the role of CXCR4 and its inhibitor AMD3100 in colon-bladder cross-organ sensitization. The colitis model was established by rectal infusion of trinitrobenzene sulfonic acid. Western blot and immunofluorescence were used to assess the expression and distribution of CXCR4. Intrathecal injection of AMD3100 (a CXCR4 inhibitor) and PD98059 (an ERK inhibitor) were used to inhibit CXCR4 and downstream extracellular signal-regulated kinase (ERK) in the spinal cord and dorsal root ganglion (DRG). Intravesical perfusion of resiniferatoxin was performed to measure the pain behavior counts of rats, and continuous cystometry was performed to evaluate bladder voiding function. Compared to the control group,

CXCR4 was expressed more in bladder mucosa and colon mucosa, L6-S1 dorsal root ganglion (DRG), and the corresponding segment of the spinal dorsal horn (SDH) in rats with colitis. Moreover, intrathecal injection of the AMD3100 suppressed bladder overactivity, bladder hyperalgesia, and mastocytosis symptoms caused by colitis. Furthermore, AMD3100 effectively inhibited ERK activation in the spinal cord induced by experimental colitis. Finally, treatment with PD98059 alleviated bladder overactivity and hyperalgesia caused by colitis. Increased CXCR4 in the DRG and SDH contributes to colon inflammation-induced bladder overactivity and hyperalgesia partly via the phosphorylation of spinal ERK. Treatment targeting the CXCR4/ERK pathway might provide a potential new approach for the comorbidity between the digestive system and the urinary system.

[AN EXPERIMENTAL MODEL OF THE EPITHELIAL TO MESENCHYMAL TRANSITION AND PRO-FIBROGENESIS IN UROTHELIAL CELLS RELATED TO BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS](#)

Xing-Wei Jin, Qi-Zhang Wang, Yang Zhao, Bo-Ke Liu, Xiang Zhang, Xian-Jin Wang, Guo-Liang Lu, Jun-Wei Pan, Yuan Shao. Transl Androl Urol. 2021 Nov;10(11):4120-4131. doi: 10.21037/tau-21-392. PMID: 34984178 PMCID: PMC8661263 DOI: 10.21037/tau-21-392

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Suitable in vitro models are needed to investigate urothelial epithelial to mesenchymal transition (EMT) and pro-fibrogenesis phenotype in bladder pain syndrome/interstitial cystitis (BPS/IC). This study from China aimed to establish a novel experimental BPS/IC cell model and explore how different concentrations of tumor necrosis factor (TNF)- α influence the EMT and pro-fibrogenesis phenotype of urothelial cells. SV-HUC-1 urothelial cells were cultured with 2, 10, or 50 ng/mL TNF- α to mimic chronic inflammatory stimulation. The EMT and pro-fibrogenesis phenotype, including production of collagen I and pro-fibrosis cytokines, were estimated after 72 h of culture. The bladder urothelial cells of BPS/IC exhibited upregulated vimentin, TNF- α and TNF receptor, downregulated E-cadherin, and increased collagen I. Higher concentrations of TNF- α (10 and 50 ng/mL) produced an obvious mesenchymal morphology, enhanced invasion and migratory capacity, increased expression of vimentin, and decreased expression of E-cadherin. Collagen I was increased in cells treated with 2 and 10 ng/mL TNF- α after 72 h. Secretion of interleukin (IL)-6 and IL-8 was promoted with 10 and 50 ng/mL TNF- α , while that of IL-1 β or transforming growth factor- β was unaffected. Slug and Smad2 were upregulated by TNF- α after 72 h. The Smad pathway was activated most strongly with 10 ng/mL TNF- α and Slug pathway activation was positively correlated with the concentration of TNF- α . Sustained 10 ng/mL TNF- α stimulation induced the EMT and pro-fibrogenesis phenotype resembling BPS/IC in SV-HUC-1 cells. Minor inflammatory stimulation induced the pro-fibrogenesis phenotype while severe inflammatory stimulation was more likely to produce significant EMT changes. Different degrees of activation of the Slug and Smad pathways may underlie this phenomenon.

[THERAPEUTIC INTERVENTIONS TO UROLOGIC CHRONIC PELVIC PAIN SYNDROME AND UPOINT SYSTEM FOR CLINICAL PHENOTYPING: HOW FAR ARE WE?](#)

Muhammad Naveed, Li Changxing, Awais Ullah Ihsan, Muhammad Shumzaid, Asghar Ali Kamboh, Ali Asghar Mirjat, Muhammad Saeed, Mirza Muhammad Faran Ashraf Baig, Hafiz Muhammad Zubair, Sobia Noreen, Asadullah Madni, Zhou Xiaohui. Urologia. 2022 Jan 3;3915603211065301. doi: 10.1177/03915603211065301. PMID: 34978224 DOI: 10.1177/03915603211065301

The assessment and management of urologic chronic pelvic pain syndrome (UCPPS), is controversial. It is classified by voiding symptoms, pelvic pain, and bladder pain, which is weekly treated, weekly understood, and bothersome. In the aspect of clinical efforts and research to help people with this syndrome have been hampered by the deficiency of a widely reliable, accepted, and a valuable tool to evaluate the patient symptoms and quality of life (QoL) impact. However, the etiology comes into sight is multifactorial, and available treatment options have been imprecise considerably in present years. The authors from China and Pakistan compiled the published literature on the assessment of the syndrome, a tentative role of pharmacological and non-pharmacological (conservative, alternative, and invasive therapy) interventions in eradicating the disease as well as improving symptoms. The previously published literature on animal models has established the association of immune systems in the etiology, pathogenesis, and progression of the disease. The UPOINT system for clinical phenotyping of UCPPS patients has six predefined domains that direct multimodal therapy, which would lead to significant symptom improvement in the medical field. The narrative review aims to scrutinize the fluctuating scientist's views on the evaluation of patient and multimodal treatment of the UPOINT system.

[USING SOCIAL MEDIA TO CROWDSOURCE COLLECTION OF URINE SAMPLES DURING A NATIONAL PANDEMIC](#)

Elijah P Ward, Sarah N Bartolone, Prasun Sharma, Michael B Chancellor, Laura E Lamb. *Int Urol Nephrol.* 2022 Jan 26. doi: 10.1007/s11255-022-03108-5. Online ahead of print. PMID: 35080680 DOI: 10.1007/s11255-022-03108-5

The COVID-19 pandemic and subsequent lockdown had a substantial impact on normal research operations. Researchers needed to adapt their methods to engage at-home participants. One method is crowdsourcing, in which researchers use social media to recruit participants, gather data, and collect samples. The authors utilized this method to develop a diagnostic test for IC/BPS. Participants were recruited via posts on popular social-media platforms and enrolled via a website. Participants received and returned a mail kit containing bladder symptom surveys and a urine sample cup containing room-temperature preservative. Using this method, we collected 1254 IC/BPS and control samples in 3 months from all 50 United States. Their data demonstrate that crowdsourcing is a viable alternative to traditional research, with the ability to reach a broad patient population rapidly. Crowdsourcing is a powerful tool for at-home participation in research, particularly during the lockdown caused by the COVID-19 pandemic.

TRYPSIN-INDUCED ELEVATED CONTRACTILE RESPONSES IN A RAT MODEL OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: INVOLVEMENT OF PAR2 AND INTRACELLULAR CA²⁺ RELEASE PATHWAYS

Denizalti Merve, Anjum Irfan, Simsek Gul, Onder Sevgen Celik, Durlu-Kandilci Nezahat Tugba. *Life Sci.* 2022 Jan 26;120359. doi: 10.1016/j.lfs.2022.120359. Online ahead of print. PMID: 35092732 DOI: 10.1016/j.lfs.2022.120359

IC/BPS is a chronic inflammatory disease with unclear etiology. Different receptors play a role in the pathophysiology including protease activated receptors (PARs). This study from Turkey investigated the subtypes and the effects of PARs on contractility using permeabilized detrusor smooth muscle strips in IC/BPS. IC/BPS was induced by cyclophosphamide injection. Histopathological analysis, PCR for detecting PAR proteins, western blotting for indicating PAR2 protein expression levels and myograph recording for measuring contractile force were used. In rat bladder, PAR1 and PAR2 but not PAR4 were found to be expressed. The first evidence was revealed where trypsin-induced contractions in rat permeabilized detrusor were potentiated in CYP-induced cystitis. Moreover, the functional inhibition of trypsin-induced contractions by selective PAR2 antagonist (ENMD-1068) and the supporting immunoblotting results emphasized that the main PAR subtype involved in IC/BPS model in rat bladder is PAR2. These data emphasize the prominent role of IP3 in cystitis pathology besides ryanodine channels. Trypsin-induced Ca²⁺sensitization contractions were also higher in cystitis. Both Rho kinase and protein kinase C played a role in this increased Ca²⁺sensitization situation. This paper highlights the intracellular pathways that are involved in trypsin-induced contractions mainly via PAR2 in permeabilized bladder detrusor smooth muscle in a rat model of IC/BPS.

MEDICAL CANNABIS FOR GYNECOLOGIC PAIN CONDITIONS: A SYSTEMATIC REVIEW

Angela L Liang, Erin L Gingher, Jenell S Coleman. *Obstet Gynecol.* 2022 Feb 1;139(2):287-296. doi: 10.1097/AOG.0000000000004656. PMID: 35104069 DOI: 10.1097/AOG.0000000000004656

The endocannabinoid system is involved in pain perception and inflammation. Cannabis contains delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which are cannabinoids that bind to endocannabinoid system receptors. A fatty acid amide called palmitoylethanolamide (PEA) enhances endogenous cannabinoids. Given that use of medical cannabis is increasing, Liang and colleagues from the USA sought to characterize patterns of cannabis use for gynecologic pain and its effectiveness as an analgesic. They searched PubMed, EMBASE, Scopus, Cochrane, and ClinicalTrials.gov using terms for "woman," "cannabis," and "pain" or "pelvic pain" or "endometriosis" or "bladder pain" or "cancer." The search was restricted to English-language articles published between January 1990 and April 2021 and excluded animal studies. Studies were included if they evaluated nonpregnant adult women who used cannabinoids for gynecologic pain conditions (eg, chronic pelvic pain, vulvodynia, endometriosis, interstitial cystitis, malignancy). The initial search yielded 5,189 articles with 3,822 unique citations. Fifty-nine studies were considered for full review, and 16 met inclusion criteria. Prevalence of cannabis use ranged from 13% to 27%. Most women ingested or inhaled cannabis and used cannabis multiple times per week, with dosages of THC and CBD up to 70 mg and 2,000 mg, respectively. Sixty-one to 95.5% reported pain relief. All six prospective cohort studies and one RCT of PEA-combination medications reported significant pain relief, and the average decrease in pain after 3 months of treatment was 3.35±1.39 on the 10-point visual analog scale. However, one fatty acid amide enzyme inhibitor RCT did not show pain reduction. Survey data showed that most women reported that cannabis improved pain from numerous gynecologic conditions. Cohort studies and an RCT using PEA-combination medications reported pain reduction. However, interpretation of the studies is limited due to varying cannabis formulations, delivery methods, and dosages that preclude a definitive statement about cannabis for gynecologic pain relief.

COMPONENTS OF THE ENDOGENOUS CANNABINOID SYSTEM AS POTENTIAL BIOMARKERS FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Saki Sultana, Geraint Berger, Christian Lehmann. *Diagnostics (Basel)*. 2021 Dec 23;12(1):19. doi: 10.3390/diagnostics12010019. PMID: 35054185 DOI: 10.3390/diagnostics12010019

IC/BPS is a chronic condition causing bladder pressure and pain, is of unknown etiology and often accompanied by other symptoms, including chronic pelvic pain, increased urinary urgency, and frequency. There is no definitive diagnosis for IC/BPS, and treatment options are currently limited to physical therapy and medications to help alleviate symptoms. The endogenous cannabinoid system (ECS) is an important regulator of numerous physiological systems, including the urinary system. Modulations of the ECS have been shown to be beneficial for IC/BPS-associated pain and inflammation in rodents. As an attempt to identify potential biomarkers for IC/BPS, the authors from Canada reviewed experimental studies where the components of the ECS have been quantified in experimental models of IC/BPS. Further investigations using well-defined animal models and patients' data are required to obtain stronger evidence regarding the potential for ECS components to be definitive biomarkers for IC/BPS.

IMPROVED UROTHELIAL CELL PROLIFERATION, CYTOSKELETON AND BARRIER FUNCTION PROTEIN EXPRESSION IN THE PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AFTER INTRAVESICAL PLATELET-RICH PLASMA INJECTION

Jia-Fong Jhang, Yuan-Hong Jiang, Yung-Hsiang Hsu, Han-Chen Ho, Lori A Birder, Teng-Yi Lin, Hann-Chorng Kuo. *Int Neurourol J*. 2022 Jan 20. doi: 10.5213/inj.2142100.050. Online ahead of print. PMID: 35073671 DOI: 10.5213/inj.2142100.050

This study investigated urothelial cell proliferation, cytoskeleton, inflammation, and barrier function protein expressions in patients with IC/BPS after intravesical platelet-rich plasma (PRP) injections. 19 patients with IC/BPS underwent 4 monthly intravesical PRP injections. Bladder biopsies were taken at the first and fourth PRP treatment. The bladder specimens were analyzed using the Western blot and immunochemical staining for progenitor cell markers for sonic hedgehog (Shh), CD34, and cytoskeleton proteins CK5, CK14, CK20; barrier function markers for zonula occludens-1 (ZO-1), E-cadherin, and intercellular adhesive molecule-1, tryptase and transforming growth factor- β (TGF- β). Global response assessment (GRA) was used to evaluate treatment outcomes. The mean age of patients was 55.6 years. After PRP injections, the functional bladder capacity and maximum flow rate increased, and the visual analog scale (VAS) of pain, IC symptom index, IC problem index, O'Leary-Sant symptom score, and GRA improved in all patients. Urothelium Shh, CK5, ZO-1, E-cadherin, and TGF- β expressions increased significantly after repeated PRP injections. By subgrouping, according to PRP treatment outcomes, significant increases in Shh, E-cadherin, and ZO-1 expressions were noted only in patients with GRA ≥ 1 or improved VAS, but not in patients with GRA=0 and no improvement in VAS. The level of urothelial barrier function protein and cell proliferation protein expression in the patients with IC/BPS was increased after repeat intravesical PRP injections. Intravesical repeat PRP injections may have potential to improve urothelial health and result in symptoms improvement in the patients with IC/BPS.

INTERSTITIAL CYSTITIS SYMPTOMS AS DEFINED ARE INDISTINGUISHABLE FROM POSTERIOR FORNIX SYNDROME SYMPTOMS CURED BY UTEROSACRAL LIGAMENT REPAIR

Petros P, Richardson P. *Pelviperrineology* 2021;40(3):145-153. <http://www.pelviperrineology.org/> open access journal. DOI: 10.34057/PPj.2021.40.02.2021-7-5

The purpose of this retrospective study from Australia was to test the authors' hypothesis that female interstitial cystitis (IC) and Posterior Fornix Syndrome (PFS) are one and the same. The authors extracted raw CPP data from patients who had TFS surgery for cure of uterine/apical prolapse, along with bladder, pad and urodynamic data. They compared known IC phenotypes with PFS symptoms to check our hypothesis for truth or falsity. They used a validated Integral Theory System Questionnaire (ITSQ), "simulated operations" testing with the speculum test (which reduces urge and pain if USLs are weak), transperineal ultrasound, urodynamics, surgery and post-operative urodynamics. Forty-six patients with CPP had 157 urinary symptoms. The cure rate was CPP 76%, urge incontinence 74%, abnormal emptying/retention 80%, nocturia 75%, frequency 50%. The authors concluded that PFS data accord exactly with the ICS definitions for IC, except that PFS patients were cured or improved by USL repair, while IC patients were not. They suggest that further testing of their hypothesis will require wide-ranging testing with the ITSQ (which diagnoses both PFS and IC), and the simulated operations "speculum tests" to confirm that USL weakness is indeed the cause.

YouTube TM AS A SOURCE OF INFORMATION ON BLADDER PAIN SYNDROME: A CONTEMPORARY ANALYSIS

Simone Morra, Claudia Collà Ruvolo, Luigi Napolitano, Roberto La Rocca, Giuseppe Celentano, Gianluigi Califano, Massimiliano Creta, Marco Capece, Carmine Turco, Simone Cilio, Alberto Melchionna, Gerardo Gerundo, Francesco Trama, Francesco Mangiapia, Ferdinando Fusco, Vincenzo Mirone, Nicola Longo. Neurourol Urodyn. 2022 Jan;41(1):237-245. doi: 10.1002/nau.24802. Epub 2021 Sep 24. PMID: 34559920 DOI: 10.1002/nau.24802

The purpose of this study from Italy was to evaluate the quality of YouTube™ videos on bladder pain syndrome (BPS) and to investigate whether they can be used as a reliable source of information. The search term "bladder pain syndrome" was used on YouTube™ platform. The first 100 videos were selected. Patient Education Materials Assessment Tool for audio-visual content (PEMAT A/V), Global Quality Score (GQS), Misinformation tool, and DISCERN score were used to assess videos' quality content. Pearson's test was used to assess potential correlations between variables. Seventy-nine videos were suitable for the analyses. The median PEMAT A/V Understandability score and PEMAT A/V Actionability score were 66.7% and 75.0%, respectively. According to GQS, 26 (32.9%), 32 (40.5%), 3 (3.8%), 15 (19.0%), and 3 (3.8%) videos were excellent, good, moderate, generally poor, and poor, respectively. According to Misinformation tool, of all videos, 81% (n = 64), 6.3% (n = 5), 5.1% (n = 4), 5.1% (n = 4), 2.5% (n = 2) had respectively no, very little, moderate, high, and extreme misinformation. The overall median DISCERN score ranged from 5.0 (IQR: 2.0-5.0) to 5.0. A positive statistically significant correlation was found between video length and PEMAT A/V Understandability, video length and PEMAT A/V Actionability, and video length and DISCERN Question 16. Nowadays, the overall quality of YouTube™ videos on BPS have been evaluated good according to PEMAT A/V, GQS, Misinformation tool, and DISCERN score. It is possible to assume that YouTube™ may be considered as a reliable source of information on BPS.

HUNNER LESION

CYSTECTOMY FOR PATIENTS WITH HUNNER-TYPE INTERSTITIAL CYSTITIS AT A TERTIARY REFERRAL CENTER IN JAPAN

Yoshiyuki Akiyama, Aya Niimi, Yasuhiko Igawa, Akira Nomiya, Yuta Yamada, Yusuke Sato, Taketo Kawai, Daisuke Yamada, Haruki Kume, Yukio Homma. Low Urin Tract Symptoms. 2021 Oct 26. doi: 10.1111/luts.12416. Online ahead of print. PMID: 34704374 DOI: 10.1111/luts.12416

The purpose of this study from Japan was to evaluate the outcomes of partial and total cystectomy in patients with refractory Hunner-type interstitial cystitis (HIC). Patients with end-stage HIC who underwent supratrigonal partial cystectomy with augmentation ileocystoplasty (PC-CP) or total cystectomy with ileal conduit (TC-IC) were identified retrospectively. Changes in the 11-point numerical rating scale of bladder pain and in 7-grade quality of life (QOL) scores were evaluated. Changes in the O'Leary and Sant's Symptom Index (OSSI) and O'Leary and Sant's Problem Index (OSPI) were analyzed in patients with PC-CP. Peri- and postoperative complications and patient satisfaction with overall outcomes were examined. Four patients (one female) underwent PC-CP and 13 (nine females) underwent TC-IC. Bladder pain persisted in three PC-CP patients but resolved completely in all TC-IC patients. Pain scale and QOL scores improved significantly in patients with TC-IC ($P < .01$), but not in those with PC-CP. OSSI/OSPI scores did not improve significantly in patients with PC-CP. Three PC-CP patients required clean intermittent catheterization due to voiding dysfunction or persistent pain. Two TC-IC patients developed stricture of the ureteroileal anastomosis, resulting in permanent placement of a ureteral stent in one case and nephrostomy in the other. Satisfaction rate was higher in the TC-IC than in the PC-CP group (76.9% vs 25.0%, $P < .05$). TC-IC provided reliable pain relief and improved QOL in patients with end-stage HIC, but the small case number and limited methodology restrict interpretation of the results. Further studies are needed to identify appropriate candidates and optimal surgical procedures.

OVEREXPRESSION OF HIF1A IN HUNNER LESIONS OF INTERSTITIAL CYSTITIS: PATHOPHYSIOLOGICAL IMPLICATIONS

Yoshiyuki Akiyama, Jimpei Miyakawa, Michael A O'Donnell, Karl J Kreder, Yi Luo, Daichi Maeda, Tetsuo Ushiku, Haruki Kume, Yukio Homma. Urol. 2021 Oct 25;101097JU0000000000002278. doi: 10.1097/JU.0000000000002278. Online ahead of print. PMID: 34694138 DOI: 10.1097/JU.0000000000002278

The purpose of this Japanese study was to elucidate biological changes in Hunner lesions, which underlie the pathophysiology of Hunner-type interstitial cystitis, by characterizing their whole transcriptome and immunopathological profiles. Paired bladder mucosal biopsies, one sample each from the Hunner lesion and non-lesion area, were obtained from 25 patients with Hunner-type interstitial cystitis. The samples were subjected to whole-transcriptome profiling; immunohistochemical quantification of CD3, CD4, CD8, CD20, CD138, mast cell tryptase, cytokeratin, and HIF1 α ; and quantitative polymerase chain reaction for IFN- α , IFN- β , IFN- γ , TNF, TGF- β 1, HIF1 α , IL-2, IL-4, IL-6, IL-10, and IL-12A. The results were compared between the lesion and non-lesion areas. RNA sequencing identified 109 differentially expressed genes and 30 significantly enriched

biological pathways in Hunner lesions. Up-regulated pathways (N=24) included "HIF1 α signalling pathway", "PI3K-Akt signalling pathway", "RAS signalling pathway", and "MAPK signalling pathway." By contrast, down-regulated pathways (N=6) included "basal cell carcinoma" and "protein digestion and absorption". The mRNA levels of HIF1 α , IFN- γ , and IL-2 and the HIF1 α protein level were significantly higher in lesion areas. Otherwise, there were no significant differences between the lesion and non-lesion samples in terms of mRNA levels of inflammatory cytokines or histological features such as lymphoplasmacytic and mast cell infiltration, epithelial denudation, and CD4/CD8 T-lymphocyte ratio. The authors conclude that their findings demonstrate significant overexpression of HIF1 α and up-regulation of its related biological pathways in Hunner lesions. The results indicate that ischemia, in conjunction with inflammation, plays a pathophysiological role in this subtype of interstitial cystitis/bladder pain syndrome, particularly in Hunner lesions.

B-DEFENSIN 2, AN ANTIMICROBIAL PEPTIDE, AS A NOVEL BIOMARKER FOR ULCERATIVE INTERSTITIAL CYSTITIS; CAN B-DEFENSIN 2 SUSPECT THE DYSBIOSIS OF URINE MICROBIOTA?

Sang Wook Lee, Si Hyun Kim, Kwang Woo Lee, Woong Bin Kim, Hae Woong Choi, Ji Eun Moon, Ahrim Moon, Young Ho Kim. Diagnostics (Basel). 2021 Nov 10;11(11):2082. doi: 10.3390/diagnostics11112082. PMID: 34829429 PMCID: PMC8619152 DOI: 10.3390/diagnostics11112082

Free full article

As urine is not sterile, inflammatory reactions caused by dysbiosis of the urinary microbiota may induce interstitial cystitis. A study was conducted in Korea to determine whether β -defensin 2 (BD-2), a specific antimicrobial peptide in the bladder, could be used as a novel diagnostic marker for ulcerative interstitial cystitis (IC). Urine samples from three female groups were examined: healthy controls (n = 34, Control group), non-Hunner type IC (n = 40, NHIC group), and Hunner type IC (n = 68, HIC group). Urine samples were collected via a transurethral catheter and assayed for BD-2 levels using enzyme linked immunosorbent assay. Under general or regional anesthesia, cystoscopy with diagnostic and therapeutic hydrodistension was performed in NHIC and HIC groups patients. These patients underwent a biopsy of the bladders. Based on the urinary specimens from 142 patients, BD-2 expression was found to be 18-fold higher in patients with Hunner type IC than in patients with non-Hunner type IC. The enhanced secretion of BD-2 exhibited a strong correlation with increased mast cell counts associated with bladder IC pathology. Enhanced urinary secretion of the antimicrobial peptide BD-2 from Hunner type IC patients associated with clinical phenotypes and demonstrated relatively robust levels to be used as a potential biomarker. Moreover, the increased urinary level of BD-2 may suggest a new possibility of biomarkers caused by dysbiosis of the urinary microbiota in ulcerative IC.

THE BACTERIAL MICROBIOTA OF HUNNER LESION INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

J Curtis Nickel, Garth D Ehrlich, Jaroslaw E Krol, Azad Ahmed, Bhaswati Sen, Archana Bhat, Joshua C Mell, R Christopher Dairon, Kerri-Lynn Kelly, Joshua P Earl. BJU Int. 2022 Jan;129(1):104-112. doi: 10.1111/bju.15519. Epub 2021 Jul 5. PMID: 34143561 DOI: 10.1111/bju.15519

The purpose of this study from Canada and the USA was to undertake the first comprehensive evaluation of the urinary microbiota associated with Hunner lesion (HL) interstitial cystitis/bladder pain syndrome (IC/BPS). Despite no previous identification of a distinct IC/BPS microbial urotype, HL IC/BPS, an inflammatory subtype of IC/BPS, was hypothesized most likely to be associated with a specific bacterial species or microbial pattern. The bacterial microbiota of midstream urine specimens from HL IC/BPS and age- and gender-matched IC/BPS patients without HL (non-HL IC/BPS) were examined using the pan-bacterial domain clinical-level molecular diagnostic Pacific Biosciences full-length 16S gene sequencing protocol, informatics pipeline and database. The authors characterized the differential presence, abundances, and diversity of species, as well as gender-specific differences between and among HL and non-HL IC/BPS patients. A total of 59 patients with IC/BPS were enrolled (29 HL, 30 non-HL; 43 women, 16 men) from a single centre and the microbiota in midstream urine specimens was available for comparison. The species abundance differentiation between the HL and non-HL groups (12 species) was not significantly different after Bonferroni adjustments for multiple comparisons. Similarly, the nine differentiating species noted between female HL and non-HL patients were not significantly different after similar statistical correction. However, four species abundances (out of the 10 species differences identified prior to correction) remained significantly different between male HL and non-HL subjects: *Negativococcus succinivorans*, *Porphyromonas somerae*, *Mobiluncus curtisii* and *Corynebacterium renale*. Shannon diversity metrics showed significantly higher diversity among HL male patients than HL female patients (P = 0.045), but no significant diversity differences between HL and non-HL patients overall. The authors report that they were not able to identify a unique pathogenic urinary microbiota that differentiates all HL from all non-HL IC/BPS. It is likely that the male-specific differences resulted from colonization/contamination remote from the bladder. They were not able to show that bacteria play an important role in patients with HL IC/BPS.

THE O'LEARY-SANT INTERSTITIAL CYSTITIS SYMPTOM INDEX IS A CLINICALLY USEFUL INDICATOR OF TREATMENT OUTCOME IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME WITH HUNNER LESIONS: A POST HOC ANALYSIS OF THE JAPANESE PHASE III TRIAL OF KRP-116D, 50% DIMETHYL SULFOXIDE SOLUTION

Naoki Yoshimura, Takashi Uno, Mitsuru Sasaki, Akira Ohinata, Shigeki Nawata, Tomohiro Ueda. *Int J Urol.* 2021 Dec 20. doi: 10.1111/iju.14765. Online ahead of print. PMID: 34929761 DOI: 10.1111/iju.14765

This study from Japan and the USA evaluated the efficacy of intravesical KRP-116D, 50% dimethyl sulfoxide solution, in interstitial cystitis/bladder pain syndrome patients with Hunner lesions (Hunner-type interstitial cystitis), and to evaluate the correlations between efficacy variables and global response assessment to determine what constitutes a minimal clinically important change. The authors performed a post hoc analysis of the Japanese phase III trial of KRP-116D. Changes at Week 12 from baseline in objective and subjective outcomes were compared between the KRP-116D and placebo groups in Hunner-type interstitial cystitis or non-Hunner-type interstitial cystitis patients. Correlations between efficacy variables at Week 12 and global response assessment were analyzed. Area under the receiver operating characteristic curve and the cut-off value of efficacy variables were calculated to determine clinically meaningful changes. The effectiveness of intravesical treatment with KRP-116D was demonstrated in Hunner-type interstitial cystitis, but not in non-Hunner-type interstitial cystitis patients. Global response assessment was closely correlated with subjective outcomes including O'Leary-Sant Interstitial Cystitis Symptom Index, O'Leary-Sant Interstitial Cystitis Problem Index, and a numeric rating scale for bladder pain, but was less correlated with voiding variables including micturition frequency, voided volume, and maximum voided volume. In the receiver operating characteristic curve analyses, the cut-off value for the O'Leary-Sant Interstitial Cystitis Symptom Index was -5 (sensitivity 81.3%, specificity 83.3%). The clinical benefit of intravesical KRP-116D in Hunner-type interstitial cystitis patients was confirmed in this post hoc analysis. A five-point reduction in O'Leary-Sant Interstitial Cystitis Symptom Index is a clinically meaningful indicator for assessing patient satisfaction with KRP-116D treatment in patients with Hunner-type interstitial cystitis.

NEUROINFLAMMATORY GENE EXPRESSION ANALYSIS REVEALS POTENTIAL NOVEL MEDIATORS AND TREATMENT TARGETS IN INTERSTITIAL CYSTITIS WITH HUNNER LESIONS

Glenn T Werneburg, Karen S Keslar, Paige Gotwald, Johnathan Doolittle, Sarah C Vij, Byron H Lee, Daniel A Shoskes. *Transl Androl Urol.* 2021 Nov;10(11):4100-4109. doi: 10.21037/tau-21-657. PMID: 34984176 PMCID: PMC8661250 DOI: 10.21037/tau-21-657

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The authors sought to study differential neuroinflammatory gene expression in men with interstitial cystitis (IC) with Hunner lesions compared with asymptomatic controls using NanoString, which uses barcoded probes to measure hundreds of genes. IC is a heterogeneous condition lacking reliable biomarkers, and a subset of patients exhibits Hunner lesions, implicating the bladder as an inflammatory pain generator. Blood, urine, and bladder biopsies were collected from 6 men with IC and Hunner lesions. 7 asymptomatic controls had blood and urine collected and 2 benign bladder biopsies were obtained from our tissue bank. RNA was isolated and analyzed with NanoString Human Neuroinflammation panel. Gene expression was considered significant if there was a >1.5-fold change and adjusted P value <0.05 compared with controls. Mean patient age was 61.5 years with 8 years median symptom duration. In bladder tissue, while many cytokine and chemokine genes had higher expression as expected (e.g., TNF, CXCL10), other significant genes included TRPA1 (1098-fold increased, expressed in pain sensing neurons) and TNFRSF17 (735-fold, B-cell related). In urine, there was 114-fold increase in S1PR4, which mediates pain via TRP-dependent pathways. A patient on cyclosporine had lower inflammatory gene expression levels relative to other IC patients, but no difference in TRPA1. Men with IC and Hunner lesions have a diverse set of neuroinflammatory genes with differential expression compared to controls. The authors identified genes linked to neuropathic pain through the TRP pathway and this expression was not reduced by cyclosporine. These findings open a new direction for biomarker and therapeutic discovery.

SUPERVISED MACHINE LEARNING ALGORITHM IDENTIFIED KRT20, BATF AND TP63 AS BIOLOGICALLY RELEVANT BIOMARKERS FOR BLADDER BIOPSY SPECIMENS FROM INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS

Tomohiko Kamasako, Kanya Kaga, Ken-Ichi Inoue, Masanori Hariyama, Tomonori Yamanishi. *Int J Urol.* 2022 Jan 31. doi: 10.1111/iju.14795. Online ahead of print. PMID: 35102612 DOI: 10.1111/iju.14795

This study from Japan was carried out to identify biomarkers that distinguish Hunner-type interstitial cystitis from non-Hunner-type interstitial cystitis patients. Total ribonucleic acid was purified from 212 punch biopsy

specimens of 89 individuals who were diagnosed as interstitial cystitis/bladder pain syndrome. To examine the expression profile of patients' bladder specimens, 68 urothelial master transcription factors and nine known markers (E-cadherin, cytokeratins, uroplakins and sonic hedgehog) were selected. To classify the biopsy samples, principal component analysis was carried out. A decision tree algorithm was adopted to identify critical determinants, in which 102 and 116 bladder specimens were used for learning and validation, respectively. Principal component analysis segregated tissues from Hunner-type and non-Hunner-type interstitial cystitis specimens in principal component axes 2 and 4. Principal components 2 and 4 contained urothelial stem/progenitor transcription factors and cytokeratins, respectively. A decision tree identified KRT20, BATF and TP63 to classify non-Hunner-type and Hunner-type interstitial cystitis specimens. KRT20 was lower in tissues from Hunner-type compared with non-Hunner-type interstitial cystitis specimens ($P < 0.001$). TP63 was lower in Hunner's lesions compared with adjacent mucosa from Hunner-type interstitial cystitis patients ($P < 0.001$). Blinded validation using additional biopsy specimens verified that the decision tree showed fairly precise concordance with cystoscopic diagnosis. KRT20, BATF and TP63 were identified as biologically relevant biomarkers to classify tissues from interstitial cystitis/bladder pain syndrome specimens. The biologically explainable determinants could contribute to defining the elusive interstitial cystitis/bladder pain syndrome pathogenesis.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: PATIENT PERSPECTIVE

[\[ICA-DEUTSCHLAND E.V.: STATUS AND OUTLOOK\].](#)

[Article in German]

Bärbel Mündner-Hensen. *Aktuelle Urol.* 2021 Dec;52(6):583-585. doi: 10.1055/a-1534-8076. Epub 2021 Nov 30. PMID: 34847609 DOI: 10.1055/a-1534-8076

The ICA-Deutschland was founded in 1993 as the first IC organisation in Europe. Since then, the association has been campaigning for more education and information for doctors and the public at the national and international levels, has initiated numerous research projects and has been able to contribute to significantly improving the diagnosis and treatment options for interstitial cystitis. On the ICA website, those affected can find detailed information about interstitial cystitis free of charge: current treatment methods, nutritional advice, patient reports, a newsletter and more. There is a lack of willingness on the part of health insurance agencies to share costs or reimbursement of costs for diagnosis and therapy measures. Even though this is regardless of the fact, that a scientifically based health care study is available, a high-quality guideline is available, many promising medical devices have been developed, an oral drug exists, approved by the EMA.

KETAMINE CYSTITIS

[LONG-TERM KETAMINE ADMINISTRATION INDUCES BLADDER DAMAGE AND UPREGULATES AUTOPHAGY-ASSOCIATED PROTEINS IN BLADDER SMOOTH MUSCLE TISSUE](#)

Yanning Li, Zhibin Dong, Gehua Wen, Xinghua Ren, Weishu Ren, Lei Yan, Xiaolong Wang, Hao Yu, Xue Wu, Xi Xia, Yan Lu, Xu Wu. *Environ Toxicol.* 2021 Dec;36(12):2521-2529. doi: 10.1002/tox.23365. Epub 2021 Sep 6. PMID: 34487425 DOI: 10.1002/tox.23365

Long-term ketamine abuse can cause significant lower urinary tract symptoms in humans, termed ketamine-associated cystitis (KC). The authors from China established a model of long-term (6 months) ketamine administration in wild-type (C57BL/6) mice. They elucidated the pathological effects of ketamine in the bladder and investigated changes in autophagy-associated protein expression (i.e., LC3, Beclin-1, and P62) and inflammatory cytokines (i.e., IL-6 and IL-1 β) in the bladder smooth muscle tissue. Long-term ketamine administration reduced the number of layers in the bladder mucosal epithelial cells (4-5 layers in the saline group vs. 2-3 layers in the ketamine groups) but increased the number of mast cells and collagen fibers. LC3-II/LC3-I, Beclin-1, IL-6, and IL-1 β protein expression in the bladder smooth muscle tissues of ketamine-treated mice was significantly increased. The mRNA and protein levels of P62 in the Ket-60 mg/kg group were also significantly increased, but not the Ket-30 mg/kg group. Their results reveal that long-term ketamine administration can cause cystitis-like pathological changes in mice, and the disordered autophagy in the bladder tissue may be involved in the persistent bladder damage following long-term administration of ketamine at 60 mg/kg.

DYSURIA VERSUS IC/BPS

[DYSURIA](#)

Parth Mehta, Stephen W. Leslie 1, Anil Kumar Reddy Reddivari. In: *StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. 2021 Dec 31. PMID: 31751108 Bookshelf ID: NBK549918*

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Dysuria is defined as the sensation of pain and/or burning, stinging, or itching of the urethra or urethral meatus associated with urination. It is a very common urinary symptom experienced by most people at least once over their lifetime. Dysuria typically occurs when urine comes in contact with the inflamed or irritated urethral mucosal lining. This is exacerbated by and associated with detrusor muscle contraction and urethral peristalsis, which then stimulates the submucosal pain receptors resulting in pain or a burning sensation during urination. Several conditions can cause dysuria via different mechanisms. True dysuria requires differentiation from other symptoms, which can also occur due to pelvic discomfort from various bladder conditions such as interstitial cystitis, prostatitis, and suprapubic or retropubic pain.

PLACEBO & NOCEBO

[THE PLACEBO AND NOCEBO EFFECTS IN FUNCTIONAL UROLOGY](#)

Hadi Mostafaei, Sandra Jilch, Greta Lisa Carlin Keiichiro Mori, Fahad Quhal, Benjamin Pradere, Ekaterina Laukhina, Victor M Schuettfort, Abdulmajeed Aydh, Reza Sari Motlagh, Claus G Roehrborn, Shahrokh F Shariat, Sakineh Hajebrahimi. *Nat Rev Urol. 2021 Dec 23. doi: 10.1038/s41585-021-00545-2. Online ahead of print. PMID: 34949831 DOI: 10.1038/s41585-021-00545-2*

A placebo is an inert substance normally used in clinical trials for comparison with an active substance. However, a placebo has been shown to have an effect on its own; commonly known as the placebo effect. A placebo is an essential component in the design of conclusive clinical trials but has itself become the focus of intense research. The placebo effect is partly the result of positive expectations of the recipient on the state of health. Conversely, a nocebo effect is when negative expectations from a substance lead to poor treatment outcomes and/or adverse events. Randomized controlled trials in functional urology have demonstrated the importance of the placebo and nocebo effects across different diseases such as overactive bladder, urinary incontinence, lower urinary tract symptoms and interstitial cystitis/painful bladder syndrome, as well as male and female sexual dysfunction. Understanding the true nature of the placebo-nocebo complex and the scope of its effect in functional urology could help urologists to maximize the positive effects of this phenomenon while minimizing its potentially negative effects.

ANIMAL MODELS - URINARY BLADDER

[REVIEW OF ANIMAL MODELS TO STUDY URINARY BLADDER FUNCTION](#)

Jing-Dung Shen, Szu-Ju Chen, Huey-Yi Chen, Kun-Yuan Chiu, Yung-Hsiang Chen, Wen-Chi Chen. *Biology (Basel). 2021 Dec 11;10(12):1316. doi: 10.3390/biology10121316. PMID: 34943231 PMCID: PMC8698391 DOI: 10.3390/biology10121316*

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The urinary bladder (UB) serves as a storage and elimination organ for urine. UB dysfunction can cause multiple symptoms of failure to store urine or empty the bladder, e.g., incontinence, frequent urination, and urinary retention. Treatment of these symptoms requires knowledge on bladder function, which involves physiology, pathology, and even psychology. There is no ideal animal model for the study of UB function to understand and treat associated disorders, as the complexity in humans differs from that of other species. However, several animal models are available to study a variety of other bladder disorders. Such models include animals from rodents to nonhuman primates, such as mice, rats, rabbits, felines, canines, pigs, and mini pigs. For incontinence, vaginal distention might mimic birth trauma and can be measured based on leak point pressure. Using peripheral and central models, inflammation, bladder outlet obstruction, and genetic models facilitated the study of overactive bladder. However, the larger the animal model, the more difficult the study is, due to the associated animal ethics issues, laboratory facility, and budget. This review aims at facilitating adapted animal models to study bladder function according to facility, priority, and disease.

URETHRAL PAIN SYNDROME

[\[STUDY OF THE STRUCTURE AND MICROFLORA OF URETHRAL TISSUES IN URETHRAL PAIN SYNDROME\]](#)

[Article in Russian]

O S Streltsova, M N Boldyreva, E B Kiseleva, Molvi A M, V F Lazukin. *Urologiia. 2021 Nov;(5):41-49. PMID: 34743430.*

Urethral pain syndrome (UPS) is characterized by the occurrence of persistent or recurrent pain in the urethra in the absence of a confirmed infection and other obvious local pathological changes. The study of its pathogenetic aspects is important first of all for understanding the causes of the disease, to prescribe effective treatment, specific recommendations for the prevention and treatment of this disease are also absent. This paper from Russia presents the advanced experience of a research group on the study of the urethral state by the in vivo cross-polarization optical coherence tomography (CP OCT) method, and also the results of the microbiota analysis in the urethral tissues. The purpose of the study was to search for the risk factors for UPS and the character of changes in the urethral tissues, using the data of: 1) concomitant pathology, 2) structural changes in the urethral wall in UPS in comparison with chronic cystitis of bacterial etiology 3) studying the microbiota of urethral tissues. The condition of the urethra was studied in 109 patients: 55 of them with UPS (group "US"), without clinical manifestations of inflammation; 41 - with chronic inflammation of the lower urinary tract of various origins (group "Inf"); in 14 patients with stones of the upper urinary tract without pyelonephritis, the urethra was taken as the norm (group "N"). All performed a clinical minimum of studies, also cystoscopy with the study of the bladder triangle, the neck of the bladder and the urethra by the method of in vivo tissue imaging - CP OCT. The device "OCT-1300U" with wavelength of 1300 nm is used. To determine the possible role of UPS disease background, the analysis of concomitant pathology preceding the development of UPS was performed. It was concluded that pilot PCR studies of biopsies from the proximal segment of the urethra indicate that low values of bacterial contamination in the majority of patients with UPS do not exclude the possible role of bacteria in the development of the disease in some patients. The CP OCT method used in this study is currently the only one in vivo method of visualization of the urethral mucosa, which provides real-time images of structural changes in the epithelial (atrophy or hyperplasia) and connective tissue (active or latent inflammation with cellular infiltration or fibrosis) layers of the urethra, allowing better understanding of the pathogenesis of the disease and monitoring of therapy.

THE SHORT-TERM EFFICACY OF ELECTRICAL PUDENDAL NERVE STIMULATION VERSUS INTRAVESICAL INSTILLATION FOR THE URETHRAL PAIN SYNDROME: A RANDOMIZED CLINICAL TRIAL

Tian Li, Xin Y Feng, Xiao M Feng, Jian W Lv, Ting T Lv, Si Y Wang. World J Urol. 2021 Oct;39(10):3993-3998. doi: 10.1007/s00345-021-03698-2. Epub 2021 May 2. PMID: 33934208 DOI: 10.1007/s00345-021-03698-2

Urethral pain syndrome is a chronic condition characterized by disturbing feeling or server pain sensed at the urethra without specific treatment. This double-center, two-arm controlled trial in China aimed to explore the efficacy of electrical pudendal nerve stimulation (EPNS) versus intravesical instillation (II) of heparin and alkalized lidocaine for urethral pain syndrome (UPS). Eighty eligible patients took three sessions of EPNS, or 1 session of II per week, for 6 consecutive weeks. The primary end point was the change of pelvic pain and urgency/frequency symptom (PUF) score from baseline to week 6. Secondary outcome measures included changes of visual analogue scale (VAS) score and three sub-score extracted from PUF score. The enrolled participants were all included in the intention-to-treat analyses, and baseline characteristics between the two groups were well balanced. It was found that, compared with the II, the EPNS results in superior pain control and better relief of lower urinary tract symptoms, and deserves further attention.

UROBIOME / MICROBIOME

UROBIOME: AN OUTLOOK ON THE METAGENOME OF UROLOGICAL DISEASES

Rachel Shoemaker, Jayoung Kim. Investig Clin Urol. 2021 Nov;62(6):611-622. doi: 10.4111/icu.20210312. PMID: 34729961 DOI: 10.4111/icu.20210312.

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The urinary tract likely plays a role in the development of various urinary diseases due to the recently recognized notion that urine is not sterile. In this mini review from Korea, the authors summarize the current literature regarding the urinary microbiome and mycobiome and its relationship to various urinary diseases. It has been recently discovered that the healthy urinary tract contains a host of microorganisms, creating a urinary microbiome. The relative abundance and type of bacteria varies, but generally, deviations in the standard microbiome are observed in individuals with urologic diseases, such as bladder cancer, benign prostatic hyperplasia, urgency urinary incontinence, overactive bladder syndrome, interstitial cystitis, bladder pain syndrome, and urinary tract infections. However, whether this change is causative, or correlative has yet to be determined. In summary, the urinary tract hosts a complex microbiome. Changes in this microbiome may be indicative of urologic diseases and can be tracked to predict, prevent, and treat them in individuals. However, current analytical and sampling collection methods may present limitations to the development in the understanding of the urinary microbiome and its relationship with various urinary diseases. Further research on

the differences between healthy and diseased microbiomes, the long-term effects of antibiotic treatments on the urobiome, and the effect of the urinary mycobiome on general health will be important in developing a comprehensive understanding of the urinary microbiome and its relationship to the human body.

PENTOSAN POLYSULFATE-ASSOCIATED MACULAR DISEASE

[ASSOCIATION BETWEEN PENTOSAN POLYSULFATE SODIUM AND RETINAL DISORDERS](#)

Gerald McGwin Jr, Paul MacLennan, Cynthia Owsley. *JAMA Ophthalmol.* 2021 Nov 18. doi:

10.1001/jamaophthalmol.2021.4778. Online ahead of print. PMID: 34792558 DOI:

10.1001/jamaophthalmol.2021.4778

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Case series have identified a macular condition hypothesized to be associated with the use of pentosan polysulfate sodium (PPS). Observational studies seeking to quantify this association have yielded equivocal results. The purpose of this study from the USA was to estimate the association between PPS exposure and maculopathy. This disproportionality analysis was conducted using the US Food and Drug Administration Adverse Event Reporting System from January 2013 through June 2020. Adverse event reports for pentosan polysulfate were selected and compared with adverse event reports associated with drugs taken for the following indications: interstitial cystitis, cystitis, bladder disorder, or bladder pain. Retinal adverse events were identified using the retinal disorders Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query, which includes conditions associated with retinal damage attributable to blockage of its blood supply, nutritional deficiencies, toxins, and diseases affecting the retina. There were 2775 reports available for analysis in the PPS group (of which 1966 were for women [70.9%]) and 6833 reports in the other drugs group (of which 4036 [59.1%] were for women). The proportion of adverse events for any macular event relative to all other events was elevated for the users of PPS compared with those using other interstitial cystitis and bladder pain drugs (proportionate reporting ratio [PRR], 1.21 [95% CI, 1.01-1.44]). With respect to specific retinal conditions, macular degeneration (20 [0.8%] vs 15 [0.2%]), maculopathy (83 [3.4%] vs 2 [0.03%]), retinal dystrophy (3 [0.1%] vs 0), retinal injury (5 [0.2%] vs 0), and retinal toxicity (3 [0.1%] vs 0) were proportionately more common among users of PPS compared with those using other interstitial cystitis and bladder pain drugs, respectively. The results of the current study add to the growing evidence that PPS use is associated with an increased risk of maculopathy. Studies that rule out prevalent retinal abnormalities prior to the initiation of PPS would strengthen the current body of literature.

ENDOMETRIOSIS AND IC/BPS

[ASSOCIATION OF ENDOMETRIOSIS WITH INTERSTITIAL CYSTITIS IN CHRONIC PELVIC PAIN SYNDROME: SHORT NARRATIVE ON PREVALENCE, DIAGNOSTIC LIMITATIONS, AND CLINICAL IMPLICATIONS](#)

Tariq F Al-Shaiji, Dalal H Alshammaa, Mariam M Al-Mansouri, Abdullatif E Al-Terki. *Qatar Med J.* 2021 Oct

7;2021(3):50. doi: 10.5339/qmj.2021.50. eCollection 2021. PMID: 34660218 PMCID: PMC8497779 DOI:

10.5339/qmj.2021.50

Chronic pelvic pain (CPP) is a diagnostic and therapeutic challenge affecting women of all ages globally. The syndrome is not well understood, but the association of interstitial cystitis (IC) with endometriosis in causing CPP should not be overlooked in managing this cohort. The authors from Kuwait present a mini review of this association to evaluate the literature in determining the prevalence of endometriosis and IC concomitantly in patients with CPP, diagnostic limitations, and clinical implications. A Medline search of the key words "evil twins' syndrome," "interstitial cystitis," "bladder pain syndrome," and "endometriosis" was conducted for full-text articles published in English over the past 20 years. The search yielded 40 articles, of which 21 were selected. Cross-referencing bibliographies of each publication yielded an additional 25 references. Both endometriosis and IC share a similar array of symptoms that are often exacerbated during the perimenstrual period. Multiple authors have reported the frequent coexistence of these two conditions. Over 80% of patients with CPP were found to have both conditions. The prevalence of endometriosis and IC coexistence was greater than that of each condition separately. It is crucial to look beyond the traditionally diagnosed endometriosis as the cause of CPP. This is true especially in patients whose previous treatment was ineffective. Simultaneous assessment for both conditions is essential to avoid the frequently delayed diagnosis and prevent unsuccessful medical and surgical therapies.

IRRITABLE BOWEL SYNDROME

PHYSICAL AND PSYCHOLOGICAL COMORBIDITIES ASSOCIATED WITH IRRITABLE BOWEL SYNDROME

Mohamed G Shiha, Imran Aziz. *Aliment Pharmacol Ther.* 2021 Dec;54 Suppl 1:S12-S23. doi: 10.1111/apt.16589. PMID: 34927759 DOI: 10.1111/apt.16589

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders encountered by physicians in primary and secondary care. Patients with IBS commonly present with various extraintestinal complaints, which account for a substantial clinical and economic burden. The common extraintestinal comorbidities associated with IBS include anxiety, depression, somatisation, fibromyalgia, chronic fatigue syndrome, chronic pelvic pain, interstitial cystitis, sexual dysfunction and sleep disturbance. The presence of comorbidity in IBS poses a diagnostic and therapeutic challenge with patients frequently undergoing unnecessary investigations and interventions, including surgery. This review from the UK discusses the different physical and psychological comorbidities associated with IBS, the shared pathophysiological mechanisms and potential management strategies.

ANORECTAL PAIN

[ANORECTAL AND PERINEAL PAIN]

[Article in German]

André Kugener, Philippe Baumann. *Ther Umsch.* 2021;78(9):533-539. doi: 10.1024/0040-5930/a001307. PMID: 34704473 DOI: 10.1024/0040-5930/a001307

Anorectal pain is a common clinical challenge in the outpatient office. Anal fissures, anal venous thrombosis, proctitis or neoplasms are frequent etiologies for proctalga. After exclusion of somatic disorders by diagnostic imaging and endoscopy, functional anorectal pain or pathologies such as interstitial cystitis, chronic prostatitis, coccydynia or pudendal neuralgia should be considered. The Rome IV criteria distinguish proctalga fugax, a sharp paroxysmal pain lasting for maximum 30 minutes, and the levator ani syndrome. The latter is characterized by a tender puborectal muscle on digital rectal examination and pain lasting for more than 30 minutes. Treatment consists in reassurance, sitz baths, topical vasodilators and anal massage. Biofeedback is a further option for levator ani syndrome. Painful palpation of the os coccygis leads to the diagnosis of coccydynia, a non-functional disorder. Therapy consists in anti-inflammatory medications, os coccygis mobilisation and infiltration therapy. Urologic chronic pelvic pain (chronic prostatitis and interstitial cystitis) as well as pudendal neuralgia, both neurogenic pelvic pain syndromes, can cause pain radiating into the after and perineum. The diagnosis and discrimination from functional rectal pain is difficult. Patients with neurogenic anorectal pain are best treated with anti-inflammatory medications, pain modulating antidepressants, anticonvulsants or local infiltration therapy. Interdisciplinary management of complex pain patients is mandatory.

COMORBIDITIES OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

[PHYSICAL AND PSYCHOLOGICAL COMORBIDITIES OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME]

[Article in German]

Regula Doggweiler, Thomas Bschiepfer. *Aktuelle Urol.* 2021 Nov 3. doi: 10.1055/a-1665-9615. Online ahead of print. PMID: 34734395 DOI: 10.1055/a-1665-9615

Compared with the healthy population, patients diagnosed with IC/BPS have a higher risk of developing further pain syndromes. Common comorbidities include endometriosis, irritable bowel syndrome, fibromyalgia, chronic fatigue, migraine, anxiety, multiple chemical sensitivity and autoimmune diseases. Chronic pain may lead to depression, which often results in social isolation. Chronic pain can only be explained and treated successfully if a person is seen as a biopsychosocial entity. Interrelations between a person and their environment are of central importance for the maintenance of health and the development of disease. The fact that the pain is located in the urogenital area makes the situation even more delicate. In this location, the authors find the functions of excretion, reproduction und sexual desire - a constellation that predisposes to a high incidence of psychosomatic events. This means that urogenital pain not only involves an unpleasant sensory experience but also feelings of fear, guilt, shame and impotence.

CORNEAL SENSATION AND NERVE FIBER CHANGES IN PATIENTS WITH INTERSTITIAL CYSTITIS

Veysel Aykut, Ipek Cigdem Ucar, Semra Akkaya Turhan, Taha Ucar, Ebubekir Durmus, Halit Oguz, Fehim Esen, Bulent Erol. *Cornea.* 2021 Oct 23. doi: 10.1097/ICO.0000000000002887. Online ahead of print. PMID: 34690263 DOI: 10.1097/ICO.0000000000002887

Central sensitization syndromes are associated with ocular surface discomfort and certain changes in corneal sensation. The aim of this study from Turkey was to evaluate corneal changes in patients with interstitial cystitis

(IC). Thirty patients with IC and 32 healthy control subjects were included in this study. All patients had a detailed ophthalmological examination including measurement of corneal sensation with Cochet-Bonnet esthesiometer, tear breakup time, Schirmer I test, and Ocular Surface Disease Index questionnaire. After these examinations, corneal subbasal nerve plexus of the patients was evaluated with in vivo corneal confocal microscopy (IVCM) and the images were analyzed using fully automated software (ACC Metrics Corneal Nerve Fiber Analyzer V.2). There was no significant difference between the groups regarding age and gender distribution. Corneal sensation was significantly higher in patients with IC, whereas tear breakup time, Schirmer I test, and Ocular Surface Disease Index scores were similar between the patients and controls. IVCM demonstrated nerve fiber loss in patients with IC. Corneal nerve fiber density, corneal nerve branch density, and corneal nerve fiber length were significantly reduced in patients with IC compared with healthy controls. Patients with IC had increased corneal sensation and decreased nerve fiber density in IVCM analysis. Corneal nerve fiber loss might decrease the induction threshold of the remaining fibers to induce peripheral sensitization, which may also trigger central sensitization in long term.

[ASSOCIATION OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME WITH STRESS-RELATED DISEASES: A NATIONWIDE POPULATION-BASED STUDY](#)

Min-Hsin Yang, Jing-Yang Huang, Sung-Lang Chen, James Cheng-Chung Wei. J Clin Med. 2021 Nov 30;10(23):5669. doi: 10.3390/jcm10235669. PMID: 34884371 PMCID: PMC8658298 DOI: 10.3390/jcm10235669

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Stress-related diseases (SRDs) are adjustment disorders triggered by stressful life changes. There is a growing body of evidence showing that stress plays an important role in the pathophysiology of IC/BPS. In the present study, the authors investigated the association between SRDs and a subsequent association of interstitial cystitis/bladder pain syndrome (IC/BPS). The authors performed a nested case-control study from the Longitudinal Health Insurance Database (LHID) of Taiwan. The two-year time-varying association between SRDs and IC/BPS was explored to distinguish the short- or long-term effects of these factors. They then conducted multiple conditional logistic regressions to evaluate the adjusted odds ratio (OR) of IC/BPS in patients with a history of SRDs. A total of 1103 IC/BPS patients and 4412 non-IC/BPS patients were analyzed. For all SRDs, the significantly increased risks were obtained in 2 years before IC/BPS diagnosis, and the higher OR was observed within 3 months before the diagnosis of IC/BPS. Multiple conditional logistic regressions showed that patients who had prior medical care for urinary tract infection, chronic obstructive pulmonary disease, peptic ulcer, inflammatory bowel syndrome, autoimmune diseases, depression, sleep disorders, and allergic rhinitis within 2 years had a significant risk of IC/BPS. The authors concluded that their study demonstrates that the health care for SRDs within the previous 2 years is associated with an increased risk of subsequent IC/BPS. The time-varying association provides an important insight that helps to identify cases with IC/BPS, especially among patients with repeated UTI visits.

ARTIFICIAL INTELLIGENCE IN UROLOGY

[APPLICATIONS OF ARTIFICIAL INTELLIGENCE IN UROLOGICAL SETTING: A HOPEFUL PATH TO IMPROVED CARE](#)

Sung-Jong Eun, Jayoung Kim, Khae Hawn Kim. J Exerc Rehabil. 2021 Oct 26;17(5):308-312. doi: 10.12965/jer.2142596.298. eCollection 2021 Oct. PMID: 34805018 PMCID: PMC8566099 DOI: 10.12965/jer.2142596.298

Artificial intelligence (AI) has been introduced in urology research and practice. Application of AI leads to better accuracy of disease diagnosis and predictive model for monitoring of responses to medical treatments. This mini-review article From Korea and USA aims to summarize current applications and development of AI in urology setting, in particular for diagnosis and treatment of urological diseases. This review will introduce that machine learning algorithm-based models will enhance the prediction accuracy for various bladder diseases including interstitial cystitis, bladder cancer, and reproductive urology.

PUDENDAL NERVE ENTRAPMENT

[RECOMMENDATIONS ON THE MANAGEMENT OF PUDENDAL NERVE ENTRAPMENT SYNDROME: A FORMALISED EXPERT CONSENSUS](#)

Amélie Levesque, Eric Baurtant, Virginie Quistrebert, Guy Valancogne, Thibault Riant, Marc Beer Gabel, Anne-Marie Leroi, Katleen Jottard, Luc Bruyninx, Gerard Amarenco, Lara Quintas, Pascale Picard, Thierry Vancaillie, Christine Leveque, Frédérique Mohy, Bruno Rioult, Stéphane Ploteau, Jean-Jacques Labat, Amandine Guinet-Lacoste, Bertrand Quinio, Michel Cosson, Rebecca Haddad & Xavier Deffieux, Marie-Aimée Perrouin-Verbe, Claire

Garreau, Roger Robert. *Eur J Pain*. 2022 Jan;26(1):7-17. doi: 10.1002/ejp.1861. Epub 2021 Oct 13. PMID: 34643963 DOI: 10.1002/ejp.1861

Since the development and publication of diagnostic criteria for pudendal nerve entrapment (PNE) syndrome in 2008, no comprehensive work has been published on the clinical knowledge in the management of this condition. The aim of this work was to develop recommendations on the diagnosis and the management of PNE. The methodology of this study was based on French High Authority for Health Method for the development of good practice and the literature review was based on the PRISMA method. The selected articles have all been evaluated according to the American Society of Interventional Pain Physicians assessment grid. The results of the literature review and expert consensus are incorporated into 10 sections to describe diagnosis and management of PNE: (1) diagnosis of PNE, (2) patients advice and precautions, (3) drugs treatments, (4) physiotherapy, (5) transcutaneous electrostimulations (TENS), (6) psychotherapy, (7) injections, (8) surgery, (9) pulsed radiofrequency, and (10) Neuromodulation. The following major points should be noted: (i) the relevance of 4+1 Nantes criteria for diagnosis; (ii) the preference for initial monotherapy with tri-tetracyclics or gabapentinoids; (iii) the lack of effect of opiates, (iv) the likely relevance (pending more controlled studies) of physiotherapy, TENS and cognitive behavioural therapy; (v) the incertitudes (lack of data) regarding corticoid injections, (vi) surgery is a long term effective treatment and (vii) radiofrequency needs a longer follow-up to be currently proposed in this indication. These recommendations should allow rational and homogeneous management of patients suffering from PNE. They should also allow to shorten the delays of management by directing the primary care. Pudendal nerve entrapment (PNE) has only been known for about 20 years and its management is heterogeneous from one practitioner to another. This work offers a synthesis of the literature and international experts' opinions on the diagnosis and management of PNE.

CHRONIC PELVIC PAIN

NEUROMUSCULAR TREATMENT APPROACH FOR WOMEN WITH CHRONIC PELVIC PAIN SYNDROME IMPROVING PELVIC PAIN AND FUNCTIONALITY

Soha Patil, Gabrielle Daniel, Rakhi Vyas, Yogita Tailor, Melanie Howell, Tayyaba Ahmed, Christian Reutter, Allyson Shrikhande. *Neurourol Urodyn*. 2022 Jan;41(1):220-228. doi: 10.1002/nau.24799. Epub 2021 Sep 16. PMID: 34529875 DOI: 10.1002/nau.24799

This study from the USA reports the effects of treating underlying myofascial dysfunction and neuropathic pain in women with chronic pelvic pain syndrome (CPPS). Retrospective longitudinal study of 186 women with CPPS treated with ultrasound-guided peripheral nerve blocks and trigger point injections to pelvic floor muscles alongside pelvic floor physical therapy once weekly for 6 weeks in an outpatient setting. Visual Analogue Scale (VAS) and Functional Pelvic Pain Scale (FPPS) questionnaires quantified pain and function in the pelvis. Working, intercourse, sleeping, walking, running, lifting, bladder, and bowel were the function categories. Statistical significance was established by p value less than .05 in paired two-sample t-test. Findings support the success of the comprehensive treatment protocol. Patients who had persistent symptoms after a full course of pelvic floor physical therapy experienced improvements in pain levels and function once it was combined with ultrasound-guided nerve blocks and trigger point injections, interactively treating underlying neuromuscular dysfunction.

URODYNAMIC AUTONOMIC BLADDER DYSFUNCTION IN WOMEN WITH COMPLEX CHRONIC PELVIC PAIN IS ASSOCIATED WITH SMALL FIBER POLYNEUROPATHY

Sarah Mozafarpour, Annie Chen, Jan Alberto Paredes Mogica, Ngozi Nwaoha, Khosro Farhad, Suzanne M Morrison, Elise J B De. *Neurourol Urodyn*. 2022 Jan;41(1):482-489. doi: 10.1002/nau.24858. Epub 2021 Dec 22. PMID: 34936711 DOI: 10.1002/nau.24858

Small fiber neuropathy/polyneuropathy (SFN) has been found to be present in 64% of complex (refractory or multisystem) chronic pelvic pain (CPP) patients. The small fiber dysfunction seen in SFN can negatively impact autonomic control of micturition in addition to pain. This study investigated the clinical association of autonomic dysfunction (detrusor underactivity and primary bladder neck obstruction [BNO]) on video urodynamics (VUDS) with SFN in patients with CPP. This was a retrospective observational study, querying data from patients with complex CPP. Inclusion criteria were: the presence of complex (refractory or multisystem) CPP, and completion of both (1) subspecialty autonomic neurology evaluation for SFN and (2) high-quality VUDS performed according to ICS standards. Autonomic bladder dysfunction (BNO or detrusor underactivity) on VUDS was compared to the presence of SFN. Thirty-two female patients with complex CPP met criteria. Of the 32, 23 (72%) were found to have SFN. Patient with autonomic bladder dysfunction (BNO or detrusor underactivity) were more likely to have SFN. Post-void residual volume was higher in the SFN group and symptoms of urge urinary incontinence were more likely to be present. Patients with complex CPP with autonomic bladder dysfunction are more likely to

have SFN. This suggests patients with complex CPP should be considered for diagnosis and treatment of SFN, particularly if BNO or detrusor underactivity is noted on VUDS evaluation.

PHARMACOGENETIC INHIBITION OF LUMBOSACRAL SENSORY NEURONS ALLEVIATES VISCERAL HYPERSENSITIVITY IN A MOUSE MODEL OF CHRONIC PELVIC PAIN

Alison Xiaoqiao Xie, Nao Iguchi, Taylor C Clarkson, Anna P Malykhina. PLoS One. 2022 Jan 25;17(1):e0262769. doi: 10.1371/journal.pone.0262769. eCollection 2022. PMID: 35077502 DOI: 10.1371/journal.pone.0262769

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This study from the USA investigated the cellular and molecular mechanisms in the peripheral nervous system (PNS) underlying the symptoms of urologic chronic pelvic pain syndrome (UCPPS) in mice. This work also aimed to test the feasibility of reversing peripheral sensitization in vivo in alleviating UCPPS symptoms. Intravesical instillation of vascular endothelial growth factor A (VEGFA) was used to induce UCPPS-like symptoms in mice. Spontaneous voiding spot assays and manual Von Frey tests were used to evaluate the severity of lower urinary tract symptoms (LUTS) and visceral hypersensitivity in VEGFA-instilled mice. Activation of bladder VEGF signalling causes sensory neural plasticity and visceral hypersensitivity in mice, confirming its role of an UCPPS biomarker as identified by the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) research studies. Pharmacogenetic inhibition of lumbosacral sensory neurons in vivo completely reversed VEGFA-induced pelvic hypersensitivity in mice, suggesting the strong therapeutic potential for decreasing primary afferent activity in the treatment of pain severity in UCPPS patients.

PHYSIOTHERAPY AND COMBINED COGNITIVE-BEHAVIOURAL THERAPY FOR PATIENTS WITH CHRONIC PELVIC PAIN SYNDROME: RESULTS OF A NON-RANDOMISED CONTROLLED FEASIBILITY TRIAL

Christian A Brünahl, Susanne G R Klotz, Christoph Dybowski, Rebecca Albrecht, Johanna Höink, Margit Fisch, Gesche Ketels, Bernd Löwe. BMJ Open. 2021 Dec 14;11(12):e053421. doi: 10.1136/bmjopen-2021-053421. PMID: 34907064 PMCID: PMC8671982 DOI: 10.1136/bmjopen-2021-053421

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The purpose of this prospective non-randomised controlled pilot study from Germany was to explore feasibility in terms of delivering and evaluating a combination of physiotherapy and psychotherapy for patients with chronic pelvic pain syndrome (CPPS) in a tertiary care facility with a specialised interdisciplinary outpatient clinic for patients with CPPS. 311 patients were approached, 60 participated. 36 patients were included in the intervention group and 24 in the control group. Fourteen participants were lost to follow-up. Participants were non-randomly allocated to the intervention group with two consecutive treatment modules (physiotherapy and cognitive behavioural therapy) with a duration of 9 weeks each or to the control group (treatment as usual). Feasibility was operationalised in terms of delivering and evaluating the therapeutic combination. Regarding eligibility as the first aspect of feasibility, willingness to participate, dropout and satisfaction were assessed; for the second aspect, standardised self-report questionnaires measuring health-related quality of life, depression severity and pain were applied. Although eligibility and willingness-to-participate rates were low, satisfaction of the participants in the intervention group was high and dropout rates were low. Results indicated a small and non-significant intervention effect in health-related quality of life and significant effects regarding depression severity and pain. It was concluded that the combination of physiotherapy and psychotherapy for patients with CPPS seems to be feasible and potentially promising with regard to effect. However, a subsequent fully powered randomised controlled trial is needed.

MANAGEMENT OF CHRONIC PRIMARY PELVIC PAIN SYNDROMES

Brian A Parsons, Andrew P Baranowski, Bary Berghmans, Jan Borovicka, Angela M Cottrell, Paulo Dinis-Oliveira, Sohier Elneil, John Hughes, Bert E J Messelink, Amanda C de C Williams, Pedro Abreu-Mendes, Valentin Zumstein, Daniel S Engeler. BJU Int. 2021 Oct 7. doi: 10.1111/bju.15609. Online ahead of print. PMID: 34617386 DOI: 10.1111/bju.15609

Management of chronic pelvic pain (CPP) remains a huge challenge for care providers and a major burden for healthcare systems. Treating chronic pain that has no obvious cause warrants an understanding of the difficulties in managing these conditions. Chronic pain has recently been accepted as a disease in its own right by the World Health Organization, with chronic pain without obvious cause being classified as chronic primary pain. Despite innumerable treatments that have been proposed and tried to date for CPP, unimodal therapeutic options are mostly unsuccessful, especially in unselected individuals. In contrast, individualised multimodal management of CPP seems the most promising approach and may lead to an acceptable situation for a large proportion of patients. In the present review, the interdisciplinary and interprofessional European Association of Urology

Chronic Pelvic Pain Guideline Group gives a contemporary overview of the most important concepts to successfully diagnose and treat this challenging disease.

FIBROMYALGIA

[LOW-DOSE NALTREXONE FOR THE TREATMENT OF FIBROMYALGIA: PROTOCOL FOR A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL](#)

Karin Due Bruun, Kirstine Amris, Henrik Bjarke Vaegter, Morten Rune Blichfeldt-Eckhardt, Anders Holsgaard-Larsen, Robin Christensen, Palle Toft. Trials. 2021 Nov 15;22(1):804. doi: 10.1186/s13063-021-05776-7. PMID: 34781989 DOI: 10.1186/s13063-021-05776-7

Low-dose naltrexone (LDN) is used widely as an off-label treatment for pain despite limited evidence for its effectiveness. A few small trials with a high risk of bias have investigated the effect of LDN on pain associated with fibromyalgia in women, but larger and more methodologically robust studies are needed. The primary aim of this randomized controlled trial from Denmark was to investigate if 12 weeks of LDN treatment is superior to placebo in reducing the average pain intensity during the last 7 days in women with fibromyalgia. A single-center, permuted block randomized, double-blind, placebo-controlled, parallel-group trial was performed in Denmark. Randomization comprised 100 women aged 18-64 years diagnosed with fibromyalgia and treated with either LDN or placebo for 12 weeks including a 4-week titration phase. The primary outcome was change in average pain intensity (during the last 7 days) from baseline to 12 weeks. Secondary outcomes were other fibromyalgia-related symptoms, i.e., tenderness, fatigue, sleep disturbance, stiffness, memory problems, depression, anxiety and measures of global assessment, physical function, impact of fibromyalgia, pain distribution, and health-related quality of life. Intention-to-treat analysis was performed, and the number of responders with a more than 15%, 30%, and 50% improvement of pain after 12 weeks was calculated for the LDN and placebo groups. Exploratory outcomes included measures of pain sensitivity, muscle performance, and biomarkers. This study contribute high-level evidence on the efficacy of low-dose naltrexone for the treatment of pain in women with fibromyalgia. Secondary outcomes include both disease-specific and generic components investigating whether LDN influences other symptoms than pain. Exploratory outcomes are included to provide greater insight into the mechanism of action of LDN and possibly a better understanding of the underlying pathology in fibromyalgia.

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